Clinical Practice Guideline on the Management of Depression in Adults

The GPC was revised in May 2023. The review concluded that the recommendations continue to be valid. Although there are therapeutic alternatives, the group that revised the CPG concluded that first-line treatment is not affected by this fact.

The procedure for the revision of the CPG can be consulted at: revision document May 2023.

It is planned to assess the need to update the CPG five years after the last revision.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

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This CPG is an aid to decision-making in health care. It is not mandatory to comply with it, nor does it replace the clinical judgment of medical staff.

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Presentation

Depression in adults is a major health problem because of its prevalence, its impact on both the quality of life of patients and the structure of their relatives and society and its role as one of the major risk factors for suicide. Therefore, depression is considered of great importance not only for the health system, but also for society.

However, under-diagnosis and lack of treatment are still a challenge in the management of depression, with a significant percentage of patients not seeking medical attention for their symptoms of depression. Conversely, overdiagnosis and overtreatment of this disorder is also beginning to be mentioned. In addition to the foregoing, there is known the existence of variability in its clinical management, with different approaches to treatment, referral and follow-up and a high percentage of patients responding inadequately to therapeutic strategies or with a tendency to relapse.

In 2008, the first version of the Clinical Practice Guideline on the Management of Depression in Adults was published, as part of the SNS Guidelines Programme. The length of time elapsed since then and the availability of new evidence have required an update to be prepared. This new CPG was developed by a multidisciplinary group of professionals from different areas responsible for caring for patients with depression, and the review process has received the cooperation of various scientific societies and associations directly involved with this health problem. This guideline is a result of this work and aims to be a useful tool with answers to the most important issues in the form of systematically developed recommendations using the best available evidence.

In addition to the incorporation and integration of new evidence on diagnostic and therapeutic strategies, among the challenges included in this new version is the incorporation of the perspective of patients and relatives through a systematic review and a qualitative study. This approach allowed us to observe the impact of depression, understand it from a humanistic view and identify areas for improvement in the care process. Other notable contributions in relation to the previous guideline are the stepped care model approach and collaboration between primary and specialist care, which is critical for improving care for such a complex disorder as depression, based on current evidence. Finally, a section on the implementation of depression management recommendations in the electronic medical record has been included.

From the Directorate General for Public Health, Quality and Innovation, we would like to thank the authors for all their hard work and hope that this guide will contribute to a higher quality of care for patients with depression and their relatives.

M. MERCEDES VINUESA SEBASTIÁN
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Collaborating Organisations

Members of these organisations or associations participated in the external review:

Spanish Association of Neuropsychiatry (AEN).

Spanish Association for Clinical Psychology and Psychopathology (AEPCP).

National Association of Mental Health Nursing (ANESM).

Federation of Primary and Care Community Nursing Associations (FAECAP).

Galicia Federation of Families and Persons with Mental Illness (Galicia FEAFES).

Spanish Society of Psychiatric Epidemiology (SEEP).

Spanish Society of Family and Community Medicine (SEMFYC).

Spanish Society of Primary Care Physicians (SEMERGEN).

Spanish Society for Family Therapy Research and Development (AEI + DTF).

Spanish Society for the Advancement of Clinical Psychology and Health XXI Century (SEPCyS).

Spanish Society of Psychiatry (SEP).

Spanish Society of Biological Psychiatry (SEPB).

Spanish Society of Legal Psychiatry (SEPL).

Declaration of interest: All members of the working group, as well as those who have participated in the expert collaboration and external review, have made a declaration of interest which is presented in Annex 7.

Questions to be answered

PERSPECTIVES AND EXPERIENCES OF PATIENTS AND THEIR RELATIVES WITH DEPRESSION

1. What are the perspectives of patients and their relatives about depression and their experiences with the health care provided?

EVALUATION AND SCREENING OF DEPRESSION

2. How should depression be evaluated?

3. Which scales have the best psychometric properties for the evaluation of depression in adults?

4. Does screening improve health outcomes in depression?

CARE MODELS

5. How effective are stepped and collaborative care models?

PSYCHOTHERAPEUTIC TREATMENT

6. How effective are different psychological interventions in patients with depression?

PHARMACOLOGICAL TREATMENT

7. What is the safety and efficacy of antidepressant drugs in the treatment of depressive episodes in adults?

8. How long and at what dose should drug treatment be maintained after remission of depressive symptoms?

PSYCHOTHERAPEUTIC STRATEGIES IN RESISTANT DEPRESSION

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PHARMACOLOGICAL STRATEGIES IN RESISTANT DEPRESSION

10. What pharmacological strategies are most effective in patients with treatment-resistant depression?

ELECTROCONVULSIVE THERAPY

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VAGUS NERVE STIMULATION

12. What is the safety and efficacy of vagus nerve stimulation as adjunctive treatment for resistant depression?

TRANSCRANIAL MAGNETIC STIMULATION

13. What is the safety and efficacy of transcranial magnetic stimulation as adjunctive treatment for resistant depression?

EXERCISE

14. Is physical exercise effective in patients with depression?

ST JOHN'S WORT

15. What is the safety and efficacy of St. John's wort in the treatment of adult depression?

QUALITY INDICATORS

16. What are the indicators for monitoring quality in the management of depression?

IMPLEMENTATION

17. What is the progress and impact of clinical decision support and knowledge management systems on the management of depression?

SIGN Levels of evidence and grades of recommendation

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1^{++} directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1^{+} and showing overall consistency of results.
B	A body of evidence consisting of studies rated as 2^{++}, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1^{++} or 1^{+}.
C	A body of evidence consisting of studies rated as 2^{+} directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2^{++}.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2^{+}.

Studies classified as 1^{-} and 2^{-} must not be used in the preparation of recommendations due to their high potential for bias.

The recommendations adapted from a CPG are indicated with the superscript "CPG".

Q[1]	Evidence taken from relevant qualitative studies of appropriate quality. This category is not considered by SIGN.
Good clinical practice	
√[2]	Recommended practice based on clinical experience and consensus of the editorial team.

Source: Scottish Intercollegiate Guidelines Network. Forming guideline recommendations. In: SIGN 50: A guideline developers'' handbook: Edinburgh: SIGN; 20081.[1]

1. Evaluating the quality of qualitative studies was performed following the CASP (Critical Appraisal Skills Programme)[2] checklist, as proposed by Goldsmith et al. (2007)[3].

2. Sometimes the development group wishes to highlight an important practical aspect for which there is probably no supporting evidence. In general, these cases are related to an aspect of treatment generally accepted to be good clinical practice, and are evaluated as a point of good clinical practice. These messages are not an alternative to the recommendations based on evidence, but should be considered only when there is no other way of highlighting that aspect.

CPG Recommendations

Evaluation of depression

√	The clinical interview is the essential procedure for the diagnosis of depression. The ICD and DSM provide a set of agreed criteria to rely on.
C	Due to the existence of different factors that may affect the progress, course and severity of depression, it is recommended to evaluate the following areas: – Features of the episode: duration, number and intensity of symptoms, comorbidity. – Psychosocial assessment (social support and interpersonal relationships). – Degree of associated dysfunction and/or disabilities. – Risk of suicide. – Response to previous treatment.
C	It is recommended to assess the risk of suicide in patients with depression, considering the following factors: – Presence of previous suicide attempts, other comorbid mental disorders and substance abuse. – Specific symptoms such as hopelessness, anxiety, agitation or suicidal ideation. – Other risk factors such as physical illness, chronicity, pain or disability, family history of suicide, social factors and a history of suicide in the environment.
Q	When assessing depression, it is recommended to consider the heterogeneity of its presentation as well as the perception patients have about their symptoms and the disorder.
Q	It is recommended to pay special attention to issues that affect the daily lives of patients with depression which may have a greater functional impact.
Q	The assessment should consider the sociodemographic and cultural factors that may affect the development or maintenance of depressive symptoms and influence treatment, such as sex, family, social network and perceived stigma.
Q	The meaning and impact of depression on the patient's family and any needs that may arise should be explored; especially regarding children, adolescents and family dependent upon the depressed patient.
Q	It is recommended to encourage the communication of feelings and emotions in an empathetic and respectful environment.
Q	When a diagnosis of depression is made, all the necessary information about the disorder and treatment options, as well as explanations to reduce the guilt and stigma attached, must be promoted and provided.

Evaluation instruments

√	The scales provide additional information in the evaluation, but cannot replace the clinical interview.
D	Some of the scales that may be useful in assessing depression are the *Hamilton Rating Scale for Depression* (HRSD), the *Montgomery Asberg Depression Rating Scale* (MADRS), the Brief Patient Health Questionnaire (PHQ-9) and the Beck Depression Inventory (BDI).

Depression screening

B	Routine screening for depression is not recommended for the general population, as there are reasonable doubts about its effectiveness.
B	Clinicians should be alert to the possibility of depression, especially in patients with risk factors who also have symptoms such as insomnia, low mood, anhedonia and suicidal ideation.
B	In primary care, when an indicator for depression is observed in a routine examination, it is recommended to use two questions about mood and loss of enjoyment to assess for the presence of depressive disorders. If the response is positive, an appropriate psychopathological assessment is recommended.

Care models

B	The management of depression in adults should be performed as a stepped care and collaboration model between primary care and mental health, so that interventions and treatments are tailored to the status and evolution of the patient.

General treatment recommendations

√	The treatment of depression in adults should be comprehensive and cover all psychotherapeutic, psychosocial and pharmacological interventions which may improve well-being and functional capacity.
√	The management of depression should include psychoeducation, individual and family support, coordination with other professionals, care of comorbidity and regular monitoring of mental and physical status.
√	The initial selection of the mode and scope of treatment should be based on clinical findings and other factors, such as previous history, the availability of treatment, patient preference and the ability to provide support and containment in the environment.
D^{CPG}	A structured patient monitoring plan should be established. The assessment and monitoring frequency of symptoms should be according to severity, comorbidity, cooperation with treatment, social support and the frequency and severity of side effects of the prescribed treatment.
Q	With the consent of the patients, both they and their relatives and relatives should take an active role in making decisions about the treatment and care plan development.
Q	Patients and their relatives should be offered support to develop coping strategies, and should be informed of the existence of patient associations and resources which can be of help.
D^{CPG}	Verbal information should be backed up with written documents whenever possible.

Psychotherapeutic treatment

√	The availability of psychotherapeutic treatment should be ensured for patients who need it.
B	In mild-moderate depression, a brief psychological treatment (such as cognitive behavioural therapy or problem-solving therapy) of 6-8 sessions over 10-12 weeks should be considered.
B	The psychological treatment of choice for moderate to severe depression is cognitive behavioural therapy or interpersonal therapy, of 16-20 sessions over 5 months.
B	Cognitive behavioural therapy should be considered for patients with inadequate response to other interventions or a prior history of relapses and/or residual symptoms.
C	Other psychological interventions should be considered when addressing comorbidity or the complexity of family or marital relationships, often associated with depression.
B	Patients with chronic and/or recurrent depression are recommended a combination of drug therapy and cognitive behavioural therapy.

Pharmacotherapy

√	Before starting antidepressant treatment, patients must be adequately informed of the expected benefits, side effects and possible delay in the therapeutic effect.
A	The initial selection of drug therapy should be based mainly on the side effect profile and tolerability, safety and pharmacological properties, as well as other factors such as previous response to treatment, cost and patient preferences.
A	SSRIs are antidepressants with the most evidence and better risk/benefit ratio, and should be considered as the first choice of treatment.
√	All patients with moderate depression treated with drugs should be re-assessed within 15 days of the treatment start, and within 8 days in the case of severe depression.
D^{CPG}	Benzodiazepine treatment may be considered for patients with anxiety, insomnia and/or agitation, although they should not be used for longer than 2-3 weeks to prevent the development of dependence.
√	Patients undergoing drug therapy must be closely monitored, at least for the first 4 weeks.
D	Antidepressant treatment should be maintained for at least 6 months after remission of the episode, and aspects such as previous episodes, comorbidity and the presence of other risk factors should be evaluated before deciding on withdrawal of treatment.
A	It is recommended that maintenance treatment be performed with the same dose at which the response was achieved.
D^{CPG}	To avoid withdrawal symptoms, the antidepressant treatment dose should be reduced gradually, usually over a period of 4 weeks; particularly for drugs with short half-lives like paroxetine or venlafaxine.

D[CPG]	If withdrawal symptoms occur, a diagnostic confirmation should be performed and, if the symptoms are significant, reintroducing the original antidepressant at effective doses should be considered (or the use of another antidepressant in the same class with a long half-life) and the dose gradually reduced.
Q	When drug treatment is prescribed, the patient's perception should be explored and a positive attitude will be favoured. In addition, adequate monitoring for side effects, as well as evolution of the symptoms and functional capacity, should be performed. Moreover, after obtaining patient authorisation, any doubts the family has about the treatment must be clarified to gain their support.

Psychotherapeutic strategies in resistant depression

B	A combined therapy of cognitive behavioural therapy and antidepressant pharmacotherapy is recommended for patients with resistant depression.

Pharmacological strategies in resistant depression

√	The following is recommended for patients who do not improve with initial antidepressant treatment for depression: – Review of diagnosis. – Verify compliance with taking the appropriate dosage and treatment time. – Assess the existence of disease awareness, motivation to change and possible comorbidity.
√	The following is recommended for patients with a partial response after the 3rd or 4th week: – Wait for clinical evolution until the 8th week. – Increase the drug dose to the maximum therapeutic dose.
B	If the patient does not respond by the 3rd or 4th week of treatment, any of the following strategies could be attempted: – Change of antidepressant to another in the same or a different family. – Combination of antidepressants. – Enhancement with lithium or antipsychotics.
C	When the strategy is changing the antidepressant, a different SSRI or another second-generation antidepressant should initially be evaluated. If there is no response, an antidepressant with greater side effects, such as a tricyclic or MAOI, could be assessed.
C	The combination of SSRI and mianserin or mirtazapine may be a recommendable option, bearing in mind the possibility of adverse effects.
C	Enhancement with lithium or antipsychotics, such as olanzapine, quetiapine, aripiprazole or risperidone may also be a strategy to consider, bearing in mind the possibility of greater adverse effects.

D[CPG]	When enhancement or a drug combination is used: – Be aware that these strategies usually increase adverse effects. – Select those drugs for which there is information on safety in combined use. – Document the rationale for the strategy. – Monitor carefully for adverse effects.
√	There are insufficient data to recommend enhancement with carbamazepine, lamotrigine, topiramate, valproate, pindolol, thyroid hormones, zinc or benzodiazepines.

Electroconvulsive therapy

A	Electroconvulsive therapy should be considered a therapeutic option in patients with severe depression; mainly if there is a need for a rapid response due to high suicidal intent, severe physical damage or when other treatments have failed.
√	ECT should always be given by experienced professionals, following a physical and psychiatric assessment and in a hospital setting; and informed consent is essential.
Q	The decision to use ECT should be made jointly with the patient and/or family, by taking into account factors such as diagnosis, type and severity of symptoms, medical history, risk/benefit ratio, alternative therapies and patient preference.
Q	Should ECT be required, it is recommended to place special emphasis on providing all the necessary information, focusing on the purpose of the procedure, the side effects and a treatment plan.

Vagus nerve stimulation

√	The use of vagus nerve stimulation outside the scope of research is discouraged due to the invasive nature of the procedure, uncertainty about its efficacy and adverse effects.

Transcranial magnetic stimulation

B	Transcranial magnetic stimulation is not currently recommended as a treatment for depression, due to uncertainty about its clinical efficacy.

Exercise

B	Patients with depression are strongly encouraged to perform physical exercise as a healthy living habit. It is imperative that the patient is motivated and willing to do exercise, according to their physical condition and tailored to their individual preferences.
B	Physical activity should be considered an adjunct to antidepressants and/or psychotherapy in severe and moderate depression.

St. John’s Wort

B	Although there is evidence of the efficacy of St. John's Wort in the treatment of mild to moderate depression, its use is not recommended for the following reasons: – Lack of knowledge about of the active ingredients, mechanisms of action and persistence of the antidepressant effect. – A lack of standardisation of the dose. – The variability of different commercial preparations, which may have different amounts and proportions of its components and may not be therapeutically equivalent.
B	Healthcare professionals should inform patients taking St. John's wort of its serious potential interactions with some drugs, some of which are commonly used, such as oral contraceptives.

1. Introduction

According to the World Health Organisation (WHO), depression affects about 121 million people worldwide, of whom less than 25% have access to effective treatment; and it warns that one in five people will develop depressive symptoms in their life, with this number increasing if there are other factors such as comorbidity or stress. Furthermore, because of its early onset, its functional impact and its tendency to chronicity and recurrence, depression is currently one of the leading causes of disability and represents 4.3% of the global burden of disease[4,5].

The prevalence of this disorder varies according to the country studied; thus, the American *'National Comorbidity Survey Replication'* noted that 16.2% of people had major depression at some point in their life (lifetime prevalence) and 6.6% in the last 12 months (annual prevalence)[6]. According to the *European Study of the Epidemiology of Mental Disorders* (ESEMeD), the prevalence in Spain is lower than in other European countries, with a lifetime prevalence of a depressive episode of 10.6% and a yearly prevalence of 4.0%; although one of the most notable features is that it has an earlier age of onset and high rates of comorbidity and chronicity[7.] Also, among hospitalised patients, the prevalence of depression rises to 18.9%8 and som e groups, such as illegal immigrants, are especially vulnerable, with a percentage of 40.7%[9].

People with depression have high rates of comorbidity and mortality. The association between depression and physical and mental illness, as well as with substance abuse and suicidal behaviour, is considerable. The relationship of these disorders with depression is complex, since depression predisposes their condition while, at the same time, the presence of these disorders increases the likelihood of having depression[5]. No less important is the impact functionally and on productivity, which is estimated could represent a significant portion of the costs associated with depression[10,11]. In this regard, it has been suggested that depression is the most expensive mental disorder in Europe, and accounts for 33% of the total costs of mental health, neurology and neurosurgery (118 billion euros, including direct and indirect costs), or 1% of the European economy[11]. The indirect costs due to sick leave and lost productivity account for 61% of this expenditure, while the direct costs are divided between outpatient care (61%), hospitalisation (9%), drug treatment (8%) and mortality (3%)[11].

Notwithstanding the foregoing, under-diagnosis and under-treatment remain a problem in the management of depression, both in Spain and internationally; therefore, it is a priority to optimise services and improve their approach[12-15.] In Spain, it has been estimated that 28% of patients with major depression are not diagnosed in primary care, although this percentage is lower in the more severe forms of depression[15]. Furthermore, a sample of patients with depression in the ESEMeD-Spain study showed that 59% did not attend primary care or specialist care in the previous year; and, of these, 76% received no treatment[12]. Apart from a lack of resources, other barriers to effective treatment identified by the WHO are a lack of trained professionals and the social stigma[4].

While under-diagnosis is a major problem, over-diagnosis and over-treatment of depression are also important factors to consider in the management of this disease[16,17].

The Clinical Practice Guidelines might have an important role in these areas; encouraging improved diagnostic and therapeutic strategies, the services provided and reducing variability in clinical practice.

In summary, because of its high prevalence, its impact on the health and productivity of people, the associated costs and its role as one of the major risk factors for suicide, depression is a challenge for both healthcare systems and society.

2. Scope and objectives

The first version of the Clinical Practice Guideline on the Management of Major Depression in Adults was published in 2008 as part of the Quality Plan Health Ministry for the Spanish National Health System, driven by factors such as high prevalence, disability, impaired quality of life and its enormous economic and social impact. The time elapsed since then, the magnitude of the problem, which is still significant with prospects of worsening, the increased scientific literature and the demand from the different areas involved in its approach, has led to a need to update it.

This new Clinical Practice Guideline on the Management of Depression in Adults both updates and replaces the previous guideline. It is the result of the work of a multidisciplinary group of professionals involved with the care of patients with depression, and is intended to answer many of the questions posed by the care of adult patients with depression; which will be given in the form of systematically developed recommendations based on the best evidence available today. Although research regarding the management of depression has significantly increased in recent years, there are still areas of uncertainty, so future updates of this guide addressing these issues are to be expected.

The main users of this guide will be those health professionals involved in the management of depression, as well as patients, their relatives and caregivers. This guide may also be relevant for social service professionals, although it is not specifically addressed to them.

Objectives of the guide:

- Improve the healthcare given to patients with depression in the field of primary and secondary care in the Spanish National Health System.
- Provide updated recommendations for the healthcare professionals involved in caring for patients with depression.
- Promote rationality and effectiveness in choosing the different treatment options.
- Propose a therapeutic algorithm.
- Discuss indicators to evaluate quality of care.
- Help patients, families and friends, by preparing information specifically addressed to them; thus contributing to informed decision-making and communication between patients and professionals.
- Identify priority areas for future research.

Scope of the guideline:

- The target groups will be adults diagnosed with depression.
- The professional healthcare given to these patients in both primary care and speciality care; and, in particular, aspects related to clinical diagnosis, assessment and treatment methods (psychotherapy, drug therapy, combined therapy and other interventions).

Areas not addressed by the CPG:

- Prevention of depression.
- Depression in childhood and adolescence.
- Depression in older people.
- Postnatal depression.
- Dysthymic disorder, bipolar and adaptive disorder.

3. Methodology

The methodology used to update this guideline is contained in the CPG Preparing and Updating Methodology Manuals for the National Health Service[18,19].

The steps followed were:

- Forming the working group to update the CPG, comprising two experts in methodology from the Galicia Health Technology Assessment Agency (avalia-t) and an interdisciplinary group of health professionals, composed of three psychiatrists, two clinical psychologists, a family doctor and a mental health specialist nurse.
- Updated CPG information was sent to a number of national experts along with a request to review the scope if they considered the need to add or modify any section.
- Reformulation of clinical questions using the *Patient/Intervention/Comparison/Outcome* (PICO) format.
- Inclusion of the perspective of patients and relatives by including a qualitative section on their perspectives and needs regarding depression:
    - Systematic review of qualitative studies.
    - Qualitative study based on focus groups (two with patients and one with family members) addressing the following areas:
        > Nature and impact of depression.
        > Living with depression.
        > Assessment of the professionals involved and the care process.
        > Treatment: benefits, side effects or unwanted effects, adherence and participation in decision-making.
        > Assessment of overall satisfaction with the care received.
        > Needs and preferences regarding information received and communication with the health professionals who care for them.
    - Incorporation of qualitative evidence in the CPG in a specific qualitative section and assessment and treatment sections.
- Literature database search: 1) Specialising in systematic reviews, such as the *Cochrane Library Plus* and the NHS *Centre for Reviews and Dissemination* database (HTA, DARE and NHSEED); 2) Specialising in clinical practice guidelines and other summarised resources, such as *Turning Research into Practice* (TRIP), the National Guideline Clearinghouse and GuiaSalud; 3) General, such as Medline (PubMed), EMBASE (Ovid), ISI WEB, Bibliographic Index of Health Sciences (IBECS) and the Spanish Medical Index (IME); as well as specialist, such as PsycINFO. Languages: English, French, Spanish, Italian and Portuguese. In updating the CPG, the original search strategies were used, with redesigning in some cases. For updated clinical questions, the searches were carried out from January 2007 to February 2014. For new questions, the searches were made without any time limit. In the first phase, the searches were directed toward secondary information sources, such as CPGs and systematic reviews, which were followed by

searches for primary studies limited to the most relevant studies published after the search date of the systematic reviews identified.

– Assessment of the quality of quantitative studies and the summary of evidence for each question, using the methodology proposed by the Scottish Intercollegiate Guidelines Network (SIGN)[1]. Although there is a growing tendency to use the GRADE method[20] in CPGs, the development group decided to continue with the SIGN method, as this was an update. This decision was taken primarily because a change in methodology would have required at least a partial re-evaluation of the studies included in the previous version. The qualitative studies were evaluated by following the Critical Appraisal Skills Programme (CASP)[2] checklist, as proposed by Goldsmith et al. (2007)[3].

– The formulation of recommendations was based on the SIGN "formal evaluation" or "reasoned judgment" criteria. Controversial recommendations or those with an absence of evidence were resolved by informal consensus of the development group. Recommendations based on qualitative evidence are marked with a "Q".

– The expert collaborators participated in the review and advice on specific sections of the guideline and its recommendations. The external reviewers were involved in reviewing the full draft of the guideline, with representatives proposed by the various scientific organisations and associations related with depression (see the list in the authors section), as well as renowned professionals proposed by the update development group.

– All the information on the GPC methodology applied (e.g. literature search strategies and summary tables from the selected studies) is available in detailed form at http://portal.guiasalud.es.

4. Definition, Risk factors and Diagnosis

4.1 Definition

Depression is seen as a set of mainly affective symptoms (pathological sadness, apathy, anhedonia, hopelessness, weakness, irritability, subjective feeling of distress and helplessness when faced with the demands of life). However, to varying degrees, there are also symptoms of a cognitive, volitional and somatic type, so that one might speak of an overall physical and mental affectation, with particular emphasis on the affective sphere[13,21].

Diagnosing a depressive disorder is usually based on not very specific observational data, such as a deterioration in demeanour and personal appearance, physical slowness, low voice, sad expression, easy or spontaneous crying, decreased attention, verbalisation of pessimistic ideas (e.g. guilt, hypochondria or ruin), sleep disturbances and non-specific somatic complaints. The basis for distinguishing these pathological changes from the ordinary is given by the persistence of the symptoms, their severity and the degree of functional and social impairment.

Many cases of depression are clearly visible in clinical practice, although it is difficult to establish their diagnostic autonomy from other psychopathological entities. Thus, for example, depressive disorder is often perceived to be associated with anxiety with various symptomatic combinations being manifested. Depression can also be concurrent with the abuse of alcohol or other substances or some organic brain and systemic diseases[4.] It is also frequently associated with eating behaviour disorders and some personality disorders[22]. Furthermore, it is more common among people with chronic physical illness; and the relationship between the two is mutual, as the physical problems may exacerbate depression and depression in turn may adversely affect the course of the physical pathology. Depression is also a risk factor for certain physical conditions, such as cardiovascular disease[23].

Depression can start at any age, although the highest prevalence occurs between 15 and 45 years, so it has a significant impact on education, productivity, performance and relationships[14,21]. The symptoms of the disorder may differ with age; young people show primarily behavioural symptoms, while older adults more often have somatic symptoms[24, 25].

4.2. Risk Factors

Depression is a multifactorial and complex process whose probability of development depends on a wide range of risk factors, whose multiple interactions and totality have not been able to be established until now. The importance of each in relation to the circumstances and time of life in which they develop is unknown[26].

Research into the risk factors for depression has some limitations: first, it is difficult to differentiate between the factors influencing the start and/or maintenance of depression; second, many of the risk factors interact in ways that may be causes or consequences. Moreover, few studies have assessed their degree of influence[27].

The variables that increase the risk of depression can be classified into personal, social, cognitive, familial and genetic.

Personal and social factors

The prevalence and incidence of depressive disorders is greater in females than in males, beginning in adolescence and remaining throughout adulthood[27]. In addition, although depression is a major cause of disability in both men and women, it is estimated that the burden of depression is 50% higher in women than in men[21].

Chronic diseases, both physical and mental[13] and the possible association with consumption of alcohol and tobacco[28,29] are also important risk factors.

Neurotic personality traits are associated with a higher incidence and relapses of major depression[30-32] and probably increase the likelihood of developing depression when faced with adverse life events[33]. Other forms of psychopathology are also associated, especially anxiety disorders[32]. These disorders are generally risk factors for the first episode of major depression; while dysthymia[30] has also been seen as an important predictor of later development of symptoms of major depression[34].

Moreover, it was observed that patients, mainly men with a history of panic attacks, have an increased risk of developing major depression. This correlation was not found with other mental disorders[35].

An association between migraine and depression has also been described, such that patients with major depression have a higher risk of migraine and, in turn, those with migraine (no other type of headache) have an increased risk of major depression[36.] Also, the presence of heart disease and various endocrine diseases such as diabetes, hypo- or hyperthyroidism, Cushing's syndrome, Addison's disease and hyperprolactinaemic amenorrhoea seem to increase the risk of depression[13].

Social circumstances attributed to the condition are a low level of economic resources and working circumstances[13]. Those who are unemployed or on sick leave have more frequent depressions[37]. A recently published prospective cohort study showed that people of lower socioeconomic class and low-skilled occupations have higher rates of depression, indicating that the risk of depression follows a socioeconomic gradient, especially when the disorder is chronic[38].

Marital status (being single, divorced or widowed) and chronic stress seem to be associated with a greater likelihood of developing depression[13]; while it has also been observed that exposure to adversities throughout life is involved in the onset of depressive and anxious disorders[39].

Cognitive factors

Research on the role of cognitive factors in depression has been predominantly driven by Beck's model, in which negative schemas, automatic thoughts, cognitive distortions and dysfunctional beliefs play a key role in the processing of information[40]. These and other factors, such as cognitive reactivity to negative events, the ruminative response style and attentional biases are considered key in the development and maintenance of depression[41].

Family and genetic factors

Descendants of patients with depression are a risk group for both somatic and mental disorders[42]. Thus, first-degree relatives of patients with major depressive disorder are twice as likely to have depression as the general population[43], while second-degree relatives are also significantly more likely[44]. The pattern of symptoms may also be different, with an anxiety disorder being found as an early signal[45]. However, these family studies alone cannot establish how much risk comes from genetic factors and how much comes from the shared family environment.

One of the most common approaches in the investigation of the genes involved in the development of depression is the analysis of the role of monoamines. Of all genetic variants studied, a factor that may influence the development is the presence of a polymorphism in the gene encoding the serotonin transporter, which would lead to decreased transport of this neurotransmitter[46.] This gene may be a response predictor to antidepressant treatment[47].

The predictD study conducted in 6 European countries and Chile in the primary care setting, with the aim of establishing a depression risk prediction algorithm, included the following factors: age, sex, level of education, previous depression screening results, family history of psychological problems, physical and mental health, economic difficulties and experiences of discrimination[48]. This study is currently being conducted in Spain[27,] along with a clinical trial in which the algorithm is used to quantify the degree of risk[49].

4.3 Suicide Risk

Depression is one of the factors most associated with suicidal behaviour[50,51.] It has been estimated that the risk of suicide is four times higher in people with depression compared with the general population, and 20 times higher for severe depression[51]. Because of this, different depression CPGs have included the importance of assessing the risk of suicide in a depressed patient[13, 14].

Suicidal behaviour is the result of the confluence of different situations and factors that combine together to produce a range from ideation to completed suicide. At present, it is considered that suicide moves along a continuum of different nature and severity, ranging from ideation (the idea of death as rest, death wishes and suicidal ideation) to growing behavioural gradation (threats, gestures, attempts and suicide)[51].

The risk of suicide may increase during the depressive episode and the period of partial remission[52]. Some of the factors that have been associated with increased risk of suicide in patients with depression are: male sex, family history of mental disorder, previous suicide attempt, more severe levels of depression, hopelessness and comorbid disorders, especially anxiety and the abuse of alcohol or other drugs[53]. Other factors associated with suicide in patients with depression are borderline personality disorder and high levels of impulsivity and aggression[54].

When there is a risk of suicide in depressed patients, it is recommended to consider referral to specialty care, which is urgent if the risk is high (see algorithm notes)[51].

4.4 Diagnosis

4.4.1 Diagnostic Criteria

The most well used diagnoses of depression, both clinically and in research, are those of the International Statistical Classification of Diseases and Related Health Problems (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification from the *American Psychiatric Association*[55].

International Classification of Diseases, 10th Revision (ICD-10)

The ICD-10[56] classifies major depression into mood or affective disorders (F30-F39). The category F32 is for depressive episodes and F33 for recurrent depressive disorder. The former is subdivided into the following:

- F32.0 Mild depressive episode
- F32.1 Moderate depressive episode
- F32.2 Severe depressive episode without psychotic symptoms
- F32.3 Severe depressive episode with psychotic symptoms
- F32.8 Other depressive episodes
- F32.9 Depressive episode, unspecified

In either case, the depressive episode should last at least two weeks and at least two of the three symptoms considered typical of depression must always be present (Table 1):

- Depressed mood
- Loss of interest and capacity for enjoyment
- Reduced energy

Table 1. Diagnostic criteria for a depressive episode according to ICD-10

A. The depressive episode must last at least two weeks.
B. The episode cannot be attributed to the abuse of psychoactive substances or organic mental disorder.
C. Somatic syndrome: Some of the depressive symptoms may be very prominent and acquire special clinical significance. Typically, a somatic syndrome is considered present when at least four of the following features coexist: – Marked loss of interest or pleasure in activities that were normally pleasurable – Absence of emotional reactions to events that normally produce a response – Waking up in the morning two or more hours before the usual time – Depression which is worse in the morning – Marked psychomotor retardation or agitation – Marked loss of appetite – Weight loss of at least 5% in the last month – Notable decrease of libido

Source: Adapted from WHO[56].

Table 2 shows the severity criteria of a depressive episode, according to ICD-10.

Table 2. Severity criteria of a depressive episode, according to ICD-100

A. General criteria for depressive episode: – The depressive episode must last at least two weeks. – The episode cannot be attributed to the abuse of psychoactive substances or to an organic mental disorder.
B. Presence of at least two of the following symptoms: – Clearly abnormal depressive mood for the subject, present duringmost of the day and almost every day, which is altered very little byenvironmental circumstances and which persists for at least two weeks. – Marked loss of interest or ability to enjoy activities that were previously pleasurable. – Lack of vitality or increased fatigability.
C. Up to three of the following symptoms are present: – Loss of confidence and self-esteem, and feelings of inferiority. – Disproportionate self-reproaches and feelings of excessive guilt or inadequacy. – Recurrent thoughts of death or suicide, or any suicidal behaviour. – Complaints about or decreased of the ability to concentrate and think, accompanied by a lack of decision and vacillation. – Changes of psychomotor activity, with agitation or inhibition. – Sleep disturbances of any kind. – Changes of appetite (decrease or increase) with the corresponding weight chang.
D. There may or may not be somatic syndrome*
Mild depressive episode: Two or three of the symptoms of criteria B are present. Persons with a mild episode can probably continue with their normal activities. **Moderate depressive episode**: At least 6 symptoms from criteria B and C are present, with at least two from criterion B. The person with a moderate episode will probably have difficulty keeping up with their normal activities. **Severe depressive episode:** At least 8 symptoms from criteria B and C are present, including all 3 from criterion B. People with this type of depression have marked and distressing symptoms; mainly a loss of self-esteem and feelings of guilt and worthlessness. Suicidal thoughts and actions are frequent with significant somatic symptoms. Psychotic symptoms can appear, such as hallucinations, delusions, psychomotor retardation or severe stupor. This case is calleda severe depressive episode with psychotic symptoms. Psychotic phenomena such as hallucinations or delusions may or may not be mood-congruent.

*Somatic syndrome: see Table 1. Source: Adapted from WHO[56]

American Psychiatric Association, Fifth Edition (DSM-5) Classification

The 5th edition of the DSM (Diagnostic and Statistical Manual of Mental Disorders)[57] was recently published. This new proposal divides the previous classification of "mood disorders" into "depressive disorders" and "bipolar disorders". The DSM-5 does not introduce significant changes to the DSM-IV-TR diagnostic criteria for a major depressive episode, except for the modifications and specifications to describe the current clinical status, as discussed below. The essential feature is still a period of at least 2 consecutive weeks in which the person has a minimum of 5 symptoms, of which at least one must be depressed mood or diminished interest or pleasure in all or almost all activities (Table 3). A major depressive episode can be divided into mild, moderate or severe, with specific codes for partial, total or unspecified remission (see Annex 1).

Table 3. Diagnostic criteria for major depressive disorder, according to DSM-5

A.	Five (or more) of the following symptoms have been present during a two-week period and represent a change from previous functioning; at least one of the symptoms is either (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 (as indicated by either subjective account or observation). (3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day. (4) Insomnia or hypersomnia nearly every day. (5) Psychomotor retardation or agitation 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 for 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 a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	
C. The episode is not attributable to the physiological effects of a substance or to another medical condition. D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders. E. There has never been a manic episode or hypomanic episode	

Source: Adapted from American Psychiatric Association. DSM-5[57].

The main changes to the other criteria used for diagnosing major depressive disorder are as follows:

- A reaction to or the process of grieving does not preclude the existence of a major depressive episode, so the presence of major depression must be assessed in addition to the normal response to a significant loss.
- The specifier "with mixed features" refers to at least 3 out of a list of 7 manic/hypomanic symptoms in tables of coexisting depressive symptoms. However, people whose symptoms meet the criteria for mania or hypomania will be diagnosed with bipolar I or bipolar II disorder, respectively.
- Another new specifier refers to tables of major depression occurring with anxiety symptoms. In this case, the presence of at least 2 anxiety symptoms from a list of 5 will mean the specifier "with anxiety" is added to a person.
- The specification "starting after giving birth" is changed to "starting during pregnancy", thus extending the possible presence of major depression into the pregnancy stage, as well as the first 4 weeks postpartum referred to above.
- The specification of "chronic" is moved from major depressive disorder to persistent depressive disorders (dysthymia), such that, apart from dysthymia, it includes the possibility of a chronic major depressive disorder or one with intermittent episodes; excluding the requirement of the DSM-IV-TR that the person must not have suffered a major depressive episode during the first 2 years of the disorder.
- This clinical practice guideline uses the classification and definitions of depression included in the 10th revision of the ICD-10 (Tables 1 and 2) with the codes F32 (depressive episodes) and F33 (recurrent depressive disorder); as well as the codes 296.2X (single episode) and 296.3X (recurrent episode) from the DSM-5 (Table 6). The severity of the episodes in both ICD-10 and DSM-5 are based on the number, type and severity of symptoms and the degree of functional impairment (the severity specifiers for the DSM-5 criteria appear in Annex 1).

4.4.2 Differential Diagnosis

Differential diagnosis for a depressive episode should be aimed at determining whether the oetiology is idiopathic or may be related to another medical condition, mental disorder, drug abuse or any prescribed medication.

Table 4 shows the main conditions in which depressive symptoms may occur. It is important to consider their possible presence and run the appropriate tests for these pathologies.

Table 4. Differential Diagnosis of Depression

Medical conditions	Mental Disorders
Endocrine/Metabolic Thyroid disease (hypo- or hyperthyroidism), diabetes, severe anaemia, Cushing's disease, Addison's disease, porphyria Infectious Tuberculosis, Epstein-Barr virus infection, HIV, Tertiary syphilis Neurological Alzheimer's disease, multiple sclerosis, Parkinson's disease, stroke, epilepsy Neoplasms Carcinomatosis, pancreatic cancer Others Lues, chronic pain	Panic/anxiety disorder Obsessive compulsive disorder Bipolar disorder Dysthymia Adjustment disorders Negative schizophrenic symptoms Drug consumption

Source: Prepared by the authors.

In addition, there are substances and drugs that can cause depressive symptoms, which should be taken into account when making the differential diagnosis.

5. Perspectives and experiences of patients with depression and of their relatives

Different studies have indicated important aspects of how patients understand depression and how they value the care provided. Having this information is of great importance, since the perception of patients about their illness and health services greatly influences how they access and interact with the health system[58,59].

This section includes a systematic review of qualitative studies of patients' and their relatives' experiences with depression, as well as the main results from a qualitative study conducted as part of this CPG.

Key question

- What are the perspectives of patients and of their relatives about depression and theirexperiences with the health care provided?

Systematic Review

The systematic review of the experiences of patients and their relatives which was included in the NICE[13] guideline was updated for this section. Our literature search found 3 subsequent systematic reviews: from Alderson et al.[58], Chakrabarti et al.[60] and Johansson et al.[61], as well as 22 qualitative studies not included in the previous reviews, which analysed different aspects of the perception of depression and its treatment.

The qualitative studies were evaluated using the *Critical Appraisal Skills Programme* (CASP)[2] checklist. Following the proposal of Goldsmith et al.[3], they were classified as ++ (complying with all or most of the methodological criteria), + (complying with some of the methodological criteria) and - (complying with few or none of the methodological criteria).

Information on the following topics was taken from the studies included:

- Conceptualisation (symptoms, causes and effects of depression).
- Evolution and recovery.
- Experiences with the health services and relationship with professionals.
- Experiences and perspectives of different treatment options.
- Stigma and guilt.
- Social and cultural factors.
- Role of the family.
- Vision of the family and friends.

A summary of the evidence is given below, although the results are detailed in a specific report[62].

Evidence summary

Conceptualisation: symptoms, causes and effects of depression	
Q++	Patients understand depression as a problem of self-management and as a part of their lives, rather than as a disease[13,58] and attribute it to a confluence of factors, with some of the most important being family or work/economic problems and the existence of chronic diseases[13,58,61,63,64].
Q++	The symptoms described by patients include emotional, cognitive, motivational, behavioural and somatic, including suicidal behaviour and difficulties with daily living and in social and work environments[58,65,66].
Q+	Patients identify fatigue and difficulties in personal relationships as key aspects in their day to day lives[67-69].
Q++	Being depressed has a negative impact on personal and family life as well as in the social and professional sphere[58].
Evolution and recovery	
Q+	Patients understand their depression as a chronic and cyclical process, or as a temporary process, with those in the latter group being less able to ask for help or contact the healthcare system[58,70,71].
Q++	Understanding depression, as well as being sincere and responsible towards oneself and others, are key factors in recovery[13].
Experience with health services and relationship with health professionals	
Q+	The willingness of depressed people to ask for help and their relationship with the health services can be largely explained by their perception of the disorder, and their attitudes and beliefs[59,71,72].
Q++	Patients identified the following as barriers to their diagnosis and treatment: organisations[13,73], personnel[13,58,73] and patients[13,71,74].
Q++	Their experience with primary healthcare staff is positive, although some patients expressed doubts about the ability of primary care doctors to assess their mental health and suggested a lack of time was a problem[13,73,75]. Patients also included their own lack of skills in communicating their grievances to their family doctor[13,76].
Q++	In Spain, people with depression are treated in primary care, and they emphasised the careful treatment and ongoing knowledge of different health problems. Patients treated in mental health value the expertise of psychiatrists, although they are generally linked to the prescription of drugs[77].

Treatment	
Q++	Patients consider a lack of psychotherapy as a problem in dealing with their depression[13,77], and those with more severe and complex symptoms consider they need longer-term psychotherapy[13].
Q++	One of the most valued aspects of psychotherapy is being able to discuss and find solutions to problems[58].
Q++	Most patients have confidence in the drug treatment[58,75], although their prescription often leads to ambivalent feelings, whose resolution is critical to their acceptance and adherence[13].
Q++	Some of the negative aspects of drug therapy described by patients are doubts about their effectiveness, side effects, fear of dependence and withdrawal symptoms[70,75,78.] Furthermore, because of the perceived stigma and feelings of guilt, there is a tendency to hide the drug treatment[13,70].
Q+	Variables that have been associated with adherence to drug treatment are satisfaction with the doctor, positive attitudes, high levels of information and recognition of the importance of preventing relapses[75].
Q+	The process of starting and suspending medication, guided by professionals, allows the patient to carry out self-management of the disease[70].
Q+	Information provided to patients about treatments is a key aspect[75] and the Internet is seen as an important resource[79].
Q+	In general, there is evidence of a favourable attitude towards ECT, although a minority of patients are extremely critical of it and have negative attitudes towards it[60].
Q+	Among the main benefits of ECT are a reduction in depressive symptoms and suicidal ideation[80]. Among the main negative aspects considered by patients are the lack of information, functional losses associated with this therapy, the fear of the possible brain damage it may cause and side effects, such as memory loss[60,80].
Stigma and guilt	
Q++	The perceived stigma, guilt and/or denial of diagnosis are strongly associated with the experiences of depressed patients and are a barrier to access to care and treatment[13,58,74].
Q++	Stigma has a direct impact on family, social and working relationships[58,69].

Social and cultural factors	
Q+	There are different social and cultural factors that influence patients' perception of their condition and are sometimes even identified as causal factors of depression. Sex seems to be a key one of these factors, as there are differences in how men and women understand their depression, its causes and how it is contextualised[61,64,72].
Q+	Depression has a great impact on the functioning of a family or couple, regardless of sex[81].
Role of the family from the perspective of the patient	
Q+	The role of the family is crucial, as it provides emotional support, company and support in the process[82]; however, it can also act as a barrier to treatment when the depressed person finds it difficult to communicate their feelings and symptoms[74] and when not the treatment is not supported by antidepressives[70].
Q+	A person who is depressed has a great impact on relatives, and this is a difficult situation for patients to handle, leading to hopelessness and dissatisfaction[83].
Effect on family and friends	
Q+	Being depressed leads to many difficulties in organising daily activities, a reduction in social activities and emotional instability for the whole family[67].
Q+	Each family has to develop its own coping mechanisms. Some activities such as going out together or meeting friends are beneficial and can improve the family environment[67].

Qualitative study

This section has the results of 3 focus groups, 2 conducted with patients and 1 with the family. Each group consisted of 8 people, so 24 individuals (16 patients and 8 relatives) in total participated in the study. Participants were found from 2 different sources: the Galician Health Service (specialised care) and the Federation of Associations of People with Mental Illness (FEAFES).

The methodology and results in this section are discussed more fully in a separate report[62].

The sessions lasted between about 90 and 120 minutes. The transcripts were analysed to find out the most representative aspects and experiences associated with their depression. A dual triangulation strategy of the data and researchers was used to try to provide results which were as objective as possible. As well as analysis of the discussion and categorisation of information, individual quantitative paper and pencil tasks were performed, to add to the verbal information and to mitigate any potential bias produced by those speaking longer than others, as well as possible effects of polarisation, social desirability and leadership. The sessions were moderated by two different researchers who transcribed and categorised the information independently.

As is typical of qualitative methodology, the results should always be interpreted with caution, given the known sampling limitations of such studies. Despite the lack of external validity, the results contributed to a better understanding of depression, by incorporating the experiences and feelings of the patients and family themselves with scientific knowledge. This qualitative primary information also constituted a necessary complement to the systematic review.

The views of patients and family members

Experience of depression

The concept of depression is relatively complex and confusing for both patients and relatives. However, in general, the symptoms of depression were clearly identified; with sadness, anhedonia and apathy among the most important. Suicidal ideation and behaviour are associated with the severity of the depression and are recognised as an inherent part of depression. Depression has a major impact on the lives of individuals and families, with serious consequences in the workplace and in society.

In general, depression is seen as a response to a set of factors and/or life events, rather than anything biomedical, and was most often thought to have had a trigger or precipitating event.

There is a stigma attached to depression for both patients and relatives, and there is a tendency to hide and deny the disorder. Some patients considered that "depression cannot be cured, but can be improved, although it lies dormant and can return".

An additional finding was that little is known about depression, either by patients or those in their direct environment. This lack of information leads to impotence and a lack of guidelines and strategies to follow, which not only leads to a lack of effective help but can exacerbate the problem.

"It's an awful disease... I know mine: it's anxiety, fear, it's not being able to explain what is happening to me, feeling bad, without knowing why."

"It's despair, not knowing what you have... not being able to express what is wrong with you..."

"This is depression, but family members are sometimes wrong, sometimes people with depression do not even know themselves what they have."

"Some people do not appreciate what depression is. There are many people around who do not understand …, when you're at home you try to put it into words and they don't understand. But I accept why they don't understand... "

"I was one of those who made fun of people with mental problems and when I looked at myself... I lost control of the situation, I had a very important job, and when the company went under, I just wanted to disappear myself."

"You lock yourself away, you don't want know about anyone else. Things go round in your head and you lock yourself away, until it reaches a point where you have to go to the doctor. I was taken in by it all... But it's like swimming against the tide."

"You don't understand, you often tell yourself you're depressed and you don't understand; it's a serious problem, and it affects people who suffer from it because they also feel misunderstood..."

"It's hard for anyone with this problem and also for everyone else."

"My daughter shuts herself in her room and gives no explanation, and doesn't say a word at home... She slams the door shut and that's it, nothing else to say... The worst part is that I can't do anything to help."

"At first you think it's nothing, you pay no attention to it... But you don't understand it, we want to help but it only seems to make things worse..."

"The first problem is that the person with depression sometimes doesn't want to go..."

"I said nothing about it, I always hid my depression..."

"Mine was very serious, I even attempted suicide."

"Depression has something to do with the problems that you have... either you face them or you don't; it's obvious that depression is how you respond to problems, you don't feel like doing anything, you're on the edge of committing suicide all the time."

"You have no desire to live, you feel bad that no one understands you, and that they mostly ignore you..."

Assessment of the healthcare process, treatment and staff

From the information, the care process consists of 4 main stages that require particular attention: 1) entry into the health system, 2) assessment and diagnosis, 3) treatment and 4) monitoring.

The primary care services are the gateway to health services. An enormous variability was found in the time it takes for patients to attend these. The individual nature of the disorder and its symptoms (e.g. apathy, isolation and sadness), together with the usual difficulties patients have with their environment and with recognising and responding to the problem, can mean that the first contact with the health services occurs later than would be desirable.

The initial reaction to the diagnosis is often feelings of incomprehension, impotence and difficulty in accepting it. The diagnosis is often associated with a feeling of frustration, leading to family conflicts and difficulties with living together; and there is often difficulty in starting the therapeutic process. All of these factors have a significant psychological effect on both patients and their relatives or caregivers. The heaviest demands at this point of the therapeutic process come from the sensitivity of the professionals, the time given to patients, the lack of appropriate information about the disorder, the guidelines to follow and the clinical management.

There are negative aspects associated with drug therapy (dependency, side effects, sedation, among others) and positive ones (decreased anxiety, improved sleep quality, reduction in negative ideation). Also, there is perceived to be a significant lack of information, even though this is considered especially crucial in the acute phase and an important part of dealing with and recovering from the disorder.

In general, psychotherapy is valued very positively, for its therapeutic role and the opportunity to discuss and find ways to deal with the situation. There are no significant negative aspects, although this treatment is not considered the best for everyone; and it is important to note that its effectiveness depends on factors related to personnel, such as their ability and empathy.

Monitoring is seen as a key part of the process, and yet is one of the most deficient. Both patients and relatives believe there should be closer monitoring to modify therapeutic strategies, as necessary. The perceived lack of coordination between different levels of care was also noted.

Some participants highlighted the role of private care; although this was not perceived as being of better quality, but as an alternative when care in the public system was poor.

The role of partnerships in helping patients with mental disorders and specifically patients with depression was highlighted, especially when there are other associated problems or comorbid conditions.

As for the overall assessment of the health professionals involved in the management of depression, some psychiatrists were believed to have little involvement in treatment with their role thought to be limited to prescribing drugs. The psychologist was considered as a guide, using concrete guidelines, and there were considered to be few of them in the system. Primary care physicians were considered a fundamental part of the system, although some patients felt more comfortable with being referred to specialist care when treatment was necessary. A common criticism of all staff was their lack of time, empathy and coordination and that they took no account of the family. Despite that, the professionals involved were well thought of by patients.

"First I went to my doctor and explained that I was a stamp collector and that I used to spend hours and hours on my hobby... but that now I had no enthusiasm for the things I used to like, and he referred me to a psychiatrist. My symptoms were clear: I had no sense of humour, no morale, I didn't want to go out, you're in your own world..."

"The most important thing is to have lots of regular appointments and not just now and again, especially when you're really bad."

"Sometimes the doctor only receives information from the patients and never hears other points of view from their relatives."

"As well as appointments for the patients, there should also be appointments for those close to them."

"Sometimes the family is only given information by the patient and not from the doctor."

"Psychiatrists only know how to give pills."

"For me, psychotherapy is the main part of the treatment, but all psychologists have their own way of working..."

"The psychiatrist said he could share the treatment with the psychologist, and actually that worked out very well."

"The general practitioner treats depression without referrals."

"I think you have to be comfortable with the person treating you before you can change."

"When I have had a relapse, my own doctor has treated me; and a 6-month treatment was good for me. If sometimes it's not going so well, he takes me off it and sends me to the psychiatrist... I think he works very well..."

"Health professionals should give more information."

"Many people with depression go private. I went to a private psychologist, and he didn't ask me or help me any more than the public service."

Needs and demands

The information obtained from this qualitative approach demonstrates a number of underlying needs of both patients and their family environment. These can be converted into specific demands to be met as well as possible by the health system, to continuously improve the care process:

1. Encourage the primary care services to take a more active role for early diagnosis of depression, given the difficulties and resistance patients and/or their relatives experience in receiving health care.

2. Encourage progressive destigmatisation of depression through the information and educational role of the health services.

3. Inform health professionals of the importance of maintaining an empathic and a human attitude towards the patient and family throughout the care process (especially in the early phases). This is essential so that health professionals can inspire confidence in patients throughout the entire process and thus encourage greater treatment adherence and effectiveness.

4. Improve coordination among health professionals in the different levels of care for better supervision and monitoring of each case.

5. Consider the family throughout the care process for two important reasons: for the repercussions and impact of depression on the family, and because the family is an additional source of information for better patient assessment and diagnosis. The family environment also plays a key role from a therapeutic perspective, and thus must be managed properly via appropriate information and guidelines.

6. Promote psychotherapy treatment, either alone or combined with drug treatment. Psychotherapy is clearly demanded by the patient, who has expressed the need to be heard and guided. Drug treatment alone does not meet the needs or expectations of the patient.

7. Improve monitoring of the condition and associated psychosocial factors, gradually modify drug therapy and psychotherapy and increase the number of appointments if necessary.

8. For better management of the depression by both the patient and family, it is essential to adequately respond to their demands for simple and clear information about the disorder and its treatment.

9. Provide holistic treatment for the depression, by focusing on the biomedical, psychosocial and human perspectives, as well as try to provide the necessary help to stabilise the person. At this point the role of associations is presumed to be crucial.

Recommendations[3]

Q	When assessing depression, it is recommended to consider the heterogeneity of its presentation as well as the perception patients have about their symptoms and the disorder.
Q	It is recommended to pay special attention to issues that affect the daily lives of patients with depression which may have a greater functional impact.
Q	The assessment should consider the sociodemographic and cultural factors that may affect the development or maintenance of depressive symptoms and influence treatment, such as sex, family, social network and perceived stigma.
Q	The meaning and impact of depression on the patient's family and any needs that may arise should be explored; especially regarding children, adolescents and family dependent upon the depressed patient.
Q	It is recommended to encourage the communication of feelings and emotions in an empathetic and respectful environment.
Q	When a diagnosis of depression is made, all the necessary information about the disorder and treatment options, as well as explanations to reduce the guilt and stigma attached, must be promoted and provided.
Q	It is recommended that patients and, with their consent, their families and relatives, take an active role in making decisions about treatment and the implementation of the care plan.
Q	When drug treatment is prescribed, the patient's perception of it must be explored and a positive attitude promoted towards it. Any side effects and the evolution of both symptoms and functional capacity must also be monitored. In addition, with the patient's authorisation, any doubts the family have must be clarified, to engage their support during treatment.
Q	Any decision to use ECT should be made jointly with the patient and/or family, taking into account factors such as diagnosis, type and severity of symptoms, medical history, risk/benefit ratio, alternative options and patient preferences.
Q	Should ECT be required, it is recommended to place special emphasis on providing all necessary information about the aim of the procedure, its side effects and the treatment plan.
Q	Support for patients and relatives should be offered to develop coping strategies. They must be informed of any patient associations and resources which can provide help.

[3] The recommendations of this qualitative section were integrated with the assessment and treatment sections, as these are proposed in addition to the quantitative evidence recommendations.

6. Evaluation and screening for depression

Depression may be evaluated for diagnostic purposes, when the objective is to check for the presence or absence of diagnostic criteria (usually ICD or DSM), or for screening purposes, when the frequency and severity of symptoms can be quantified.

6.1 Evaluation of depression

Key question

- How should depression be evaluated?

Although the ICD and DSM provide a set of criteria and symptoms to evaluate, these diagnostic requirements should be used to guide the interview and the clinical judgment. The clinical interview is the essential procedure in the diagnosis of depression.

The approach to evaluating depression should be comprehensive and not be based solely upon counting the number of symptoms. Because there are different factors that can affect the progression, course and severity of depression, some of the areas to be evaluated are[13,14:]

SR of different study types 2++

- Features of the episode: duration, number and intensity of symptoms, comorbidity.
- Psychosocial assessment (social support and interpersonal relationships).
- Degree of associated dysfunction and/or disabilities.
- Response to previous treatment.
- Risk of suicide.

Because major depression is one of the mental disorders most associated with suicidal behaviour, the assessment of suicide risk is a key issue. It is estimated that people with depression have a 20 times higher suicide risk than the general population84,85. As stated in the CPG for Prevention and Treatment of Suicidal Behaviour, the following should mainly be considered when assessing the risk of suicide[51]:

SR of different study types 1++, 2++, 3

- Presence of previous suicide attempts.
- Substance abuse.

– Specific symptoms such as hopelessness, anxiety, agitation or suicidal ideation.

– Other risk factors such as comorbidity, chronicity, pain or disability, family history of suicide, social factors and a history of suicide in the environment.

The timing of the assessment should also be aimed at establishing a proper relationship and therapeutic alliance[14]. SR of different study types 4

Evidence summary

2++	The approach to evaluating depression should be comprehensive and not be based solely upon counting the number of symptoms. Some of the areas to be evaluated are[13,14]: – Features of the episode: duration, number and intensity of symptoms, comorbidity. – Psychosocial assessment (social support and interpersonal relationships). – Degree of associated dysfunction and/or disabilities. – Response to previous treatment. – Assessment of safety and risk of suicide.
2++	The assessment of suicide risk in depression is important because of their frequent association[84,85].
2++	The following should be considered when assessing the risk of suicide[51]: – Presence of previous suicide attempts and substance abuse. – Specific symptoms such as hopelessness, anxiety, agitation or suicidal ideation. – Other risk factors such as comorbidity, chronicity, pain or disability, family history of suicide, social factors and a history of suicide in the environment.
4	The timing of the evaluation should also be aimed at establishing a proper relationship and therapeutic alliance[14].

Recommendations

√	The clinical interview is the essential procedure for the diagnosis of depression. The ICD and DSM provide a set of agreed criteria to rely on.
C	Due to the existence of different factors that may affect the progress, course and severity of depression, it is recommended to evaluate the following areas: – Features of the episode: duration, number and intensity of symptoms, comorbidity. – Psychosocial assessment (social support and interpersonal relationships). – Degree of associated dysfunction and/or disabilities. – Risk of suicide. – Response to previous treatment.
C	– It is recommended to assess the risk of suicide in patients with depression, considering the following factors: – Presence of previous suicide attempts, other comorbid mental disorders and substance abuse. – Specific symptoms such as hopelessness, anxiety, agitation or suicidal ideation. – Other risk factors such as physical illness, chronicity, pain or disability, family history of suicide, social factors and a history of suicide in the environment.
Q	When assessing depression, it is recommended to consider the heterogeneity of its presentation as well as the perception patients have about their symptoms and the disorder.
Q	It is recommended to pay special attention to issues that affect the daily lives of patients with depression which may have a greater functional impact.
Q	The assessment should consider the sociodemographic and cultural factors that may affect the development or maintenance of depressive symptoms and influence treatment, such as sex, family, social network and perceived stigma.
Q	The meaning and impact of depression on the patient's family and any needs that may arise should be explored; especially regarding children, adolescents and family dependent upon the depressed patient.
Q	It is recommended to encourage the communication of feelings and emotions in an empathetic and respectful environment.
Q	When a diagnosis of depression is made, all the necessary information about the disorder and treatment options, as well as explanations to reduce the guilt and stigma attached, must be promoted and provided.

6.2 Assessment instruments

Key question

- Which scales have the best psychometric properties for the assessment of depression in adults?

Scales and interviews with varying degrees of structure are used as instruments for measuring the severity of depression and response to treatment in depressive disorders. They aim to evaluate patient symptoms within a given timeframe by grading each item and giving a final score. They are not used to form a diagnosis, which is established from the psychopathological information obtained in the clinical interview.

Although different studies have shown that no systematic scales[86,87] are used in clinical practice, there is a growing consensus on the relevance of their incorporation into clinical practice, especially for monitoring the response to treatment and progression of the depression[13,14].

SR of different study types 3

Beck Depression Inventory

The Beck Depression Inventory (BDI) is one of the most used tests[88] and has validated Spanish translations in Spain for all versions: from the original 1961 version[89,] through to the revised 1978 version[90] (BDI-IA) as well as the most recent 1996 version and the second edition (BDI-II)[91], adapted by Sanz et al.[92-95]. The purpose of this tool is to detect the presence and quantify the severity of depressive symptoms.

The BDI-II is a self-reporting instrument of 21 items in which each person has to choose between four alternative responses, describing the lowest to the highest severity, that best describe their state during the previous two weeks. The four responses in each item are scored from 0 to 3 points, giving a total possible score range of 0 to 63 points (the cut-off points for the different degrees of depression in the original version and the Spanish modification are shown in Table 5).

The BDI-II version replaces the items regarding weight loss, change in body image, somatic concern and difficulties at work from the previous version (BDI-IA) with others (agitation, feelings of worthlessness, difficulty concentrating and loss of energy). In addition, the loss of appetite and insomnia items were changed so that both decreases and increases in appetite and sleep changes could be evaluated; also, changes were made to several of the statements used in assessing other symptoms. Furthermore, the period for measuring the presence and intensity of depressive symptoms was extended to two weeks.

Table 5. Cut-off points and BDI descriptors

	Minimum	Mild	Moderate	Severe
BDI-II original[91]	0-13	14-19	20-28	> 29
Spanish modification[95]	0-13	14-19	20-28	> 29
APA 2000	0-9 (no depression)	10-16	17-29	> 30
NICE 2009	0-9 (no depression)	10-16 (subclinical)	17-29 (mild to moderate)	> 30 (moderate to severe)

Source: Compiled from various sources[13,91,95]

Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (HRSD or HAM-D)[96] was designed to assess the intensity or severity of depression by clinicians, and is one of the most widely used to monitor the evolution of depressive symptoms both in clinical practice and research. The evaluation corresponds to the time frame in which it is applied, except for some items, such as sleep, which refer to the previous two days.

The original version consists of 21 items and was published in 1960[96.] There is a scaled down version by the same author of 17 items[97], another version of 24[98] and one of 6 items, referring to depressed mood, feelings of guilt, work and activities, inhibition, psychic anxiety and the somatic symptoms from the 17-item version[99]. Validation of the Spanish version was conducted in 1986100 and a psychometric assessment[101] comparing versions 6, 17 and 21 was performed later.

Adding the scores of each item Hamilton scale item provides a global severity score for depressive symptoms (the cut-off points and descriptors of different degrees of depression are shown in Table 6). Alternatively, the score from the three factors or indices can be obtained by adding the following items together: melancholy (items 1, 2, 7, 8, 10 and 13); anxiety (items 9-11) and sleep (items 4-6). There are no cut-off points established for scores on these indices.

The response to treatment is customarily defined as equal to or greater than a 50% reduction of the initial score; a partial response is between 25 and 49% and a non-response, a reduction of less than 25%[102]. Remission is considered to be achieved when the score is ≤7[103].

Table 6. Hamilton scale cut-off points and descriptors

APA 2000	No Depression	Mild	Moderate	Severe	Very Severe
NICE 2009	No Depression	Subclinical	Mild	Moderate	Severe
Score	0-7	8-13	14-18	19-22	> 23

Source: Adapted from NICE[13]

Montgomery Asberg Depression Rating Scale

The *Montgomery Asberg Depression Rating Scale* (MADRS) is applied through an interview consisting of 10 items assessing the severity of depressive symptoms[104.] The scale must be administered by a clinician, although there are various self-rating versions that have shown a moderate/good correlation with expert ratings[105].

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 for each item ranges from 0 to 6 points and the clinician can use patient information from different sources to assign the score. Compared with the HRSD, it has the advantage of not including items assessing anxiety, although it still has several somatic or vegetative items that hinder its use in patients with predominantly physical symptoms. The time frame for the assessment is the previous week or previous three days, and a Spanish version was validated in 2002[106].

As in the case of the HRDS, response to treatment was defined as a decrease in the initial score of greater than or equal to 50%, partial response is between 25 and 49% and non-response, a reduction of less 25%. Remission is considered when the score is ≤ 8-12[102].

The overall score ranges from 0-60 and is obtained from the sum of the scores assigned in each of the items. There are no defined cut-off points, but those listed in Table 6[103] are recommended.

Table 7. Recommended MADRS cut-off points and descriptors

	No Depression	**Mild**	**Moderate**	**Severe**
Recommended cut-off points	0-6	7-19	20-34	35-60
Other cut-off points in clinical trials	0-12	13-26	27-36	37-60

Source: adapted from Bobes et al.[103].

Brief Patient Health Questionnaire and Whooley questions

The *Brief Patient Health Questionnaire* (PHQ-9)[107] is the self-reported version of the depression module of the *Primary Care Evaluation of Mental Disorders Procedure* (PRIME-MD). It consists of 9 items that assess the presence of depressive symptoms (corresponding to DSM-IV criteria) over the previous 2 weeks. A diagnosis of major depression is suggested when 5 of the 9 symptoms have been present for "more than half the days" in the previous two weeks, and one of the symptoms is associated with mood or anhedonia. The suicidal ideation item is considered positive for the diagnosis regardless of its duration. The range of scores is 0-27 and each of the items ranges from 0 (never) to 3 (more than half the days). It also adds an additional question to investigate the degree of interference of the symptoms in daily life. A Spanish version has been validated and shown to have similar properties to the original[108].

Table 8. Recommended PHQ-9 cut-off points and descriptors

	Minimal or mild depressive symptoms	Mild	Moderate	Severe
Cut-off points	<10	10-14	15-19	20-27

Source: Prepared by authors.

The Whooley questions[109] are two items about mood and anhedonia in the PHQ-9 ("During the past month, have you often been bothered by feeling downhearted, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?"). However, in this version, the response is dichotomous (Yes/No) and has a cut-off point of 1. Because of its psychometric properties, it has been recommended for the identification of depression in patients with risk factors[13,110].

Other questionnaires

Table 9 shows other questionnaires used often in the assessment of depression.

Table 9. Other self-administered questionnaires used in the assessment of depression

Instrument	Items	Features	Cut-off point	Adaptation and validation in Spanish
Zung Self-Rating Depression Scale (Zung, 1965)[111]	20	Quantifies the frequency of symptoms of depression in 20 items, with cognitive and somatic symptoms having greater weight (16 items).	50	50 Conde et al. (1970)[112]; Aragones et al. (2001)[113]
Centre for Epidemiology Studies Depression Rating Scale (CES-D) (Radloff, 1977)[114]	20	Composed of 2 items assessing different symptoms of depression	16	Soler et al. (1997)[115]; Vazquez et al. (2007)[116]

Source: Prepared by authors.

Evidence summary

3	Questionnaires assessing depression may be useful in helping diagnosis or screening, as tools for assessing the severity, clinical follow-up and response to treatment[13,14].
3	Different instruments have demonstrated adequate psychometric properties for assessing depression. Among the most used are: – Beck Depression Inventory: both the original version[89] and its updates BDI-IA[90] and BDI-II[91] have been adapted and validated in Spanish[92-95]. – Hamilton Rating Scale for Depression: The original version[96,100] and comparative analysis of versions with 6[99], 17[97] and 24[98] items have been adapted and validated in Spanish. – Montgomery Asberg Depression Rating Scale[104]: There is a version validated in Spanish[106].
3	Other frequently used scales are the Brief Patient Health Questionnaire (PHQ-9)107, Zung Self-Rating Depression Scale[111] and the Centre for Epidemiologic Studies Depression Rating Scale (CES-D)[114], which have all been adapted and validated in Spanish[108,112,115,116].

Recommendations

√	The scales provide additional information in the evaluation, but cannot replace the clinical interview.
D	Some of the scales that may be useful in assessing depression are the Hamilton Rating Scale for Depression (HRSD), the Montgomery Asberg Depression Rating Scale (MADRS), the Brief Patient Health Questionnaire (PHQ-9) and the Beck Depression Inventory (BDI).

6.3 Depression Screening

Key question

- Does screening improve health outcomes in depression?

A high percentage of patients with depression are not properly diagnosed or treated[117,118,] so some authors suggest screening to ensure the identification and prescribing of appropriate treatment. However, there is no consensus on the recommendations in the guidelines and organisations from different countries.

Firstly, it is important to consider whether it would improve performance outcomes in patients with depression and whether it should be done comprehensively (the entire population, all patients under consultation) or be limited (only those patients with a specific risk). In addition, the low predictive power of the instruments used for screening has been criticised[13,14].

There is evidence of an increased number of cases of depression being found after screening programmes, although these programmes alone do not produce an improvement in the subsequent evolution of the depression[13,14,110,119].

SR of different study types 1+

The US Preventive Services Task Force (2009)[110] recommends universal screening for depression in primary care as long as it is associated with a subsequent confirmation of the diagnosis and appropriate treatment and monitoring. It does not recommend screening when subsequent monitoring is not guaranteed. This recommendation was based on a systematic review in which 8 RCTs evaluated the effectiveness of routine screening for depression coupled with further intervention vs screening without intervention and a RCT comparing different depression variables in screened and unscreened patients. They also included studies with different methodologies on the adverse effects of screening, depression treatment and the psychometric properties of different instruments. They recommended that health staff should evaluate the method they deem appropriate, according to their personal preferences, patient features and context, as there was no evidence of the effectiveness of different options. As an alternative, they proposed the use of two questions about mood and anhedonia from the Primary Care Evaluation of Mental Disorders Procedure (Whooley questions[109]: "During the past month, have you often been bothered by feeling downhearted, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?"). They also suggest that repeat screening could be effective in patients with a history of depression, unexplained somatic symptoms, comorbid mental disorders, substance abuse or chronic pain; although there is no conclusive evidence on the optimal time interval.

SR of different study types 1+, 2+, 3

The updated NICE guide[13] focuses on the systematic review of depression evaluation instruments and in identifying cases rather than the routine screening of depression. It places special emphasis in its recommendations on being alert to the possible existence of depression, particularly in cases with a past history of depression or physical illness associated with functional deficit; and it recommends the use of the two Whooley questions[109.] If the answer to any of these questions is 'yes', it recommends a psychopathological assessment and an evaluation of the need for treatment.

SR of different study types 1+, 2+, 3

Recently, the *Canadian Task Force on Preventive Health Care* (2013)[119] published an update to its 2005 recommendations on screening for depression in adults. This review, along with the previous evidence, adds 5 quasi-experimental studies (pre-post design) evaluating the effect of a community depression programme for suicide prevention in the over 65s. The update recommends not performing routine screening for depression in people with no apparent symptoms of depression, even in cases with risk factors. They exclude patients with known depression and a previous history of depression from this recommendation. However, they suggest that clinicians should be alert to the possibility of depression, especially in patients with risk factors, and should assess the presence of this disorder if there are also symptoms such as insomnia, low mood, anhedonia and suicidal ideation.

SR of different study types 1+, 2+, 3

Both the American[110] and Canadian[119] Task Force agree that there is no evidence of potential harmful effects from screening for depression, but the Canadian organisation argues that the false positives could lead to unnecessary treatment and stigma[119].

SR of different study types 1+, 2+, 3

Table 10 summarises the screening recommendations made by these organisations

Table 10. Depression screening recommendations from different organisations

Organisation	Recommendation	Screening instrument
US Preventive Services Task Force[110]	Screening for depression to be performed for adults in primary care, providing diagnosis, treatment and follow-up is ensured.	Whooley Questions[109]
UK National Institute for Health and Care Excellence[13]	Be alert to possible depression in people with a history of depression and chronic physical disease associated with disability.	Whooley Questions[109]
Canadian Task Force on Preventive Health[119]	Do not perform routine general screening for depression in people with no apparent symptoms of depression, even if there are risk factors; excluded from this recommendation are patients with a history of depression. Clinicians should be alert to the possibility of depression, especially in patients with risk factors, and should assess the presence of this disorder if there are also symptoms such as insomnia, low mood, anhedonia and suicidal ideation	None

Source: Prepared by authors.

A RCT carried out in Spain was recently published, in which the effectiveness of screening for depression in high-risk patients in primary care was evaluated. For this purpose a sample of family physicians was randomised for group intervention (n=35) or the control group (n=34). The intervention group received training on depression screening and implemented this, while the control group performed the normal management. At 6 months the effectiveness of the intervention was evaluated in a sample of 3,737 patients. No differences were found in detection or treatment rates. The observation that the programme was well accepted by clinicians, but implementation adherence was moderate, may however partly explain these results[120].

RCT 1+

Evidence summary

1+	There is evidence of an increased number of cases of depression being found after screening programmes, although these programmes alone do not produce an improvement in the subsequent evolution of the depression without other measures being implemented later[13,14,110,119].
1+	There is no evidence about any potential harmful effects of screening[110,119], although it has been suggested that false positives could lead to unnecessary treatment and stigma[119].
3	Although there is no evidence of the superiority of some psychometric instruments over others, some authors consider the Whooley questions about mood and anhedonia to be the most appropriate for screening for depression[13,110].
1+	The US Preventive Services Task Force[110] recommends universal screening for depression in primary care as long as it is associated with subsequent confirmation of the diagnosis and appropriate treatment and monitoring.
1+	The NICE guidelines recommend being alert to the possible existence of major depression, particularly in people with a history of depression and physical disease associated with disability. It proposes the Whooley questions with a time period of one month, and recommends a psychopathological assessment and evaluation of the need for treatment if at least one of the two questions is affirmative (suspected depression)[13].
1+	*The Canadian Task Force on Preventive Health Care* recommends[119] not performing routine screening for depression in people with no apparent symptoms of depression, even in cases with risk factors. They exclude patients with known depression and a previous history of depression from this recommendation. However, they suggest that clinicians should be alert to the possibility of depression, especially in patients with risk factors, and should assess the presence of this disorder if there are symptoms such as insomnia, low mood, anhedonia and suicidal ideation.
1+	A RCT conducted in Spain assessing the effectiveness of screening for depression in high-risk patients in primary care randomised a sample of family physicians to the intervention (n=35) or to a control group (n=34). The intervention group received training on depression screening and implemented this, while the control group performed the normal management. At 6 months the effectiveness of the intervention was evaluated in a sample of 3,737 patients. No differences were found in detection or treatment rates. The observation that the programme was well accepted by clinicians, but implementation adherence was moderate, may however partly explain these results[120].

Recommendations

B	Routine screening for depression is not recommended for the general population, as there are reasonable doubts about its effectiveness.
B	Clinicians should be alert to the possibility of depression, especially in patients with risk factors who also have symptoms such as insomnia, low mood, anhedonia and suicidal ideation.
B	In primary care, when an indicator for depression is observed in a routine examination, it is recommended to use two questions about mood and the ability to enjoy to assess for the presence of depressive disorders. If the response is positive, an appropriate psychopathological assessment is recommended.

7. Treatment

7.1 Depression care models and general management principles

Key question

- How effective are stepped-care and collaborative models?

There has been increasing interest in developing different care models for depression over the last twenty years. Among the most important factors driving research in this field is the recognition of depression as a chronic, disabling disease and the need to promote a shared care approach between primary and specialist care[13,121]. Although there are various models and interventions designed for this purpose, stepped-care and collaborative care models are perhaps the most promising and are discussed in this section.

7.1.1 The stepped-care model

Stepped-care treatment models have been developed to maximise effectiveness by providing less intensive interventions depending on patient status and development. Although interventions are scaled according to the complexity and severity of diseases, in general this is implicit in health care, and stepped systems are an attempt to formalise ongoing care and improve effectiveness[13].

This model has been proposed as appropriate for managing depression for several reasons. Among the most important are the evidence of equivalent results between different intensity interventions, promoting the efficient use of resources and the acceptability of intensified interventions according to severity by both professionals and patients[122].

Although stepped-care management approaches are similar, the implementation and organisation of stepped care models depend on the specific characteristics of the healthcare system; however, it is characteristic of public health services with primary care as the gateway, as occurs in Spain[121.] Some of the premises of this model are the enhancement of multidisciplinary work and collaboration between primary and specialised care. Care is stratified so that the first proposed step is the least intensive intervention in primary care; while for those cases not achieving the appropriate response after intensifying the intervention, the most appropriate level of care is specialised[123].

This treatment model is usually proposed by NICE, and both the guidelines on depression in adults and depression with chronic diseases have organised their management recommendations according to this model[13]. This organisation model for the management of depression services has also been proposed in Spain[123].

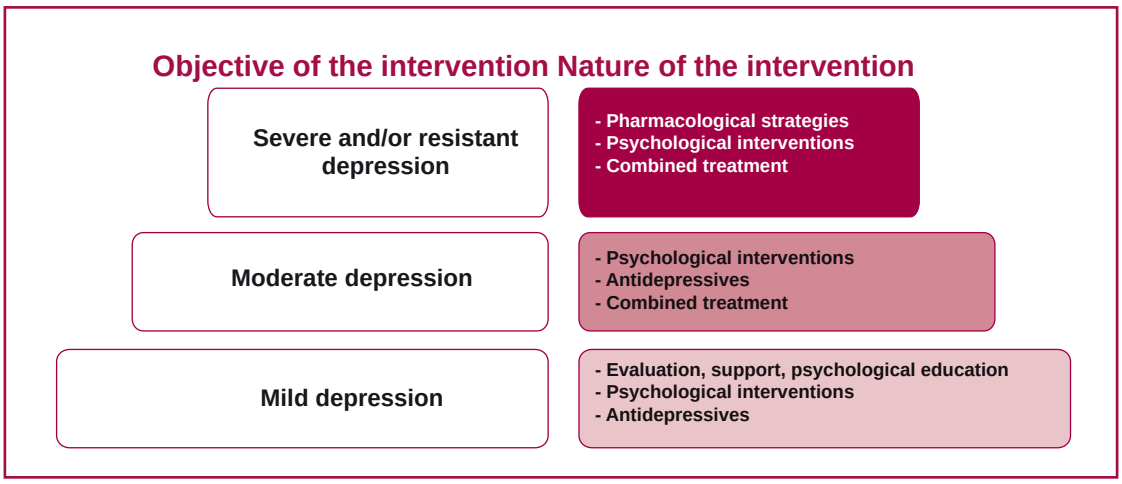
However, despite its recommendation by different organisations, there are few studies focusing specifically on evaluating the results of its adoption. Overall, the evidence for the effectiveness of these models in mental health is limited, although its inclusion as part of more complex models of collaborative care has been associated with better health results and treatment prescription[13,121]. Outside mental health, stepped-care models have been associated with health improvements in complex diseases such as chronic pain and obesity[13].

SR of different study types 1+

One of the considerations for stepped-care models is the impact they can have on the failure of initial interventions in the subsequent response to other treatments. Furthermore, although it has been suggested that high patient acceptability is among the strengths of this model, there is evidence of lower rates of entry in 2 clinical trials included in the NICE guidelines[13]. Despite these criticisms and that the evidence is inconclusive, it has been suggested that the stepped-care model in managing depression is one of the best service delivery models developed, and can guarantee access to cost-effective treatments (especially when implemented with other measures to ensure regular assessment and ease of access to interventions, among other aspects[1,3]).

SR of different study types 1+

Figure 1. Stepped-care model in managing depression



Source: Prepared by the authors from various sources[13,123].

In our health context, the implementation of a stepped-care model for depression associated with other interventions, such as professional training, use of CPG, defining the role of nursing, patient psychological education, improving communication between primary and specialist care, has been associated with improved clinical outcomes in primary care[124]. Other proposed interventions in Europe have also performed well in Spain, such as the European Programme Against Depression, based on multi-level interventions that aim to enhance collaboration in primary and specialised care[125,126].

7.1.2 Collaborative care

Collaborative care models based on the *Chronic Care Model* have been applied to improve the management of depression in primary care, where its effectiveness has been shown in improving the care process and clinical outcomes[127.] This care model: a) enhances interventions by *care managers*, usually nurses, whose main function is to improve the welfare and quality of life of people with depression; b) allows to better structure quality healthcare for the patient by planning nursing care according to the patient's needs, while integrating and coordinating the interventions from different personnel (GPs, psychiatrists, psychologists, social workers and other health professionals).

Most collaborative care systematic reviews have shown that these models are more effective than standard therapy and indicate greater effectiveness when combined with stepped care. However, the studies evaluated varied greatly in terms of the specific models, number and type of interventions and persons involved; therefore it is difficult to draw definitive conclusions[121]. SR 1+

Results from a recent meta-analysis of 37 studies comparing the collaborative model approach to depression with normal practice demonstrated the effectiveness of this model in response/remission, treatment adherence, quality of life/functional status and satisfaction with the care provided[128]. The effectiveness of the intervention was due to the following common factors: SR 1+

- Inclusion of organisational and healthcare changes in the health service system.
- Development of the role of the nurse as case and care coordination manager.
- Continuity of care through clinical monitoring of the patient.

Spain has experience of implementing a multicomponent programme based on the general principles of the chronic care model for patients (Interventions for Depression Improvement, the INDI model). This model is adapted to the organisation of care for depression within the primary care team, with a redefinition of professional roles and care circuits, with nursing playing a key role. The key points in the INDI model are: a) Training and support tools plan (e.g. clinical guidelines and algorithms) for use in decision making by doctors and nurses; b) The role of nursing: Providing psychoeducation for both the patient and family and friends; patient support for their own involvement in the process; participation in the clinical follow-up; assessment of adherence to treatment and the occurrence of adverse effects; communication of information to the attending physician; coordination between patients and primary and specialised care.

The INDI model was evaluated by a controlled trial comparing the results with standard therapy of patients with depression, where depression response and remission rates were 15-20% higher in patients treated according to the INDI model at 3 months and 1 year of follow-up[124]. RCT 1+

The same authors recently conducted a cost-utility model for INDI compared with clinical practice, and found improved incremental results for the intervention for both utility (0.045 additional QALYs) and clinical effectiveness (40.09 depression-free days, DFDs)[129]. Economic assessment study

Evidence summary

1+	Despite stepped-care models being recommended by different organisations, there are few studies focusing specifically on evaluating the results of their adoption in the management of depression. Overall, the evidence for their effectiveness is limited, although their inclusion as part of more complex models of collaborative care have been associated with better health results and treatment prescription[13,121].
1+	Most collaborative care systematic reviews have shown that these models are more effective than standard therapy and point to greater effectiveness when combined with stepped care. However, the studies evaluated varied greatly in terms of specific models, number and type of interventions and persons involved; therefore it is difficult to draw definitive conclusions[121,128].
1+	In Spain, the *Interventions for Depression Improvement* (INDI) model, a multicomponent programme based on the general principles of the chronic care models for patients, was evaluated in a randomised controlled trial by comparing it with standard therapy for patients with depression. Response and remission rates for depression were 15-20% higher in patients treated according to the INDI model at 3 months and 1 year of follow-up[124.] This model also showed a favourable cost-utility ratio, with better incremental results for the intervention regarding both utility and clinical effectiveness[129].

Recommendations

Care models	
B	The management of depression in adults should be performed as a stepped care and collaboration model between primary care and mental health, so that interventions and treatments are tailored to the status and evolution of the patient.
General treatment recommendations	
√	The treatment of depression in adults should be comprehensive and cover all psychotherapeutic, psychosocial and pharmacological interventions which may improve well-being and functional capacity.
√	The management of depression should include psychoeducation, individual and family support, coordination with other professionals, care of comorbidity and regular monitoring of mental and physical status.
√	The initial selection of the mode and scope of treatment should be based on clinical findings and other factors, such as previous history, the availability of treatment, patient preference and the ability to provide support and containment in the environment.
D^{CPG}	A structured patient monitoring plan should be established. The assessment and monitoring frequency of symptoms should be according to severity, comorbidity, cooperation with treatment, social support and the frequency and severity of side effects of the prescribed treatment.
Q	With the consent of the patients, both they and their relatives and relatives should take an active role in making decisions about the treatment and care plan development.
Q	Patients and their relatives should be offered support to develop coping strategies, and should be informed of the existence of patient associations and resources which can be of help.
D^{CPG}	Verbal information should be backed up with written documents whenever possible.

7.2 Psychotherapeutic treatment

Key question

- How effective are different psychological interventions in patients with depression?

According to the *European Association for Psychotherapy* (EAP), psychotherapy is described as comprehensive, deliberate and planned treatment or a therapeutic intervention, based on wide-ranging and specific training in behavioural disorders, diseases or wider personal development needs related to psychosocial and psychosomatic causes and factors. It uses scientific psychotherapeutic methods in an interaction of one or more individuals with one or more psychotherapists to mitigate or eliminate symptoms, change attitudes and patterns of altered behaviour, and encourage a process of maturity, development, mental health and well-being[130].

There are different models of psychotherapy that vary in aspects such as their theoretical foundation and the level of formal development of their techniques. Research in the field of psychotherapy has been increasing in recent decades and, in parallel, clinical practice guidelines on depression are consistent in recommending their use, especially those interventions developed specifically for the treatment of depression[13, 131].

Although there is consensus on the benefits of psychotherapy for adult depression, there is still debate on the comparative effectiveness of the different models. In addition, some authors are not convinced that the effects of psychotherapy may not have been overestimated due to publication bias. Thus, a meta-analytic study examined the size effect of 117 clinical trials with 175 comparisons between psychotherapy and a control, while also evaluating a number of indicators of publication bias. The authors found that the mean size of the effect was reduced by a third after adjustment for publication bias (through indirect measures)[132].

There are a number of difficulties in randomised clinical trials when it comes to testing and comparing the effectiveness of psychotherapeutic treatments:

– The existence of common factors for all psychological treatments (therapist, patient and therapeutic relationship variables), although essential as psychotherapy factors, potentially affect the results obtained in both the experimental and control groups.

– Psychological treatments are not always standardised, so there may be individual differences and slight variations that influence the result. However, treatment manuals are becoming more and more standardised.

– In most studies, the comparison group follows the normal or conventional care treatment, but this is not defined operationally, which makes comparison between groups difficult

In addition to the aforementioned difficulties, a common problem in research for different depression treatments is that outcome measurements are often based on improvements in certain scales, which are not always the same; and, generally speaking, the results include few measurements that include patient functionality.

A recent systematic review[133]evaluated all randomised trials comparing psychotherapeutic intervention (cognitive behavioural therapy, problem solving therapy, psychodynamic therapy, social skills training, counselling, interpersonal therapy and behavioural activation) with a control group (a waiting list, standard therapy or placebo) in adults with major depression. The authors identified 198 studies involving 15,118 patients and performed a meta-analysis that integrated both direct and indirect evidence from clinical trials. The 7 psychotherapies were better than being on the waiting list, with a moderate to high size effect. However, the results showed no significant differences among the different interventions, nor between individual and group formats. They also observed that, in general, greater psychotherapy benefits were found in studies that had a smaller sample size and were less stringent methodologically, with many of those included being small (only 36 of the studies had at least 50 patients receiving the same treatment). SR, 1+

7.2.1 Cognitive-behavioural therapies

Cognitive therapy, originally developed by AT Beck and formalised in the late 1970s to be applied in depression[90], has proved to be the most frequently studied psychological therapy mode for this disorder[134].

The intervention focuses on changing dysfunctional behaviours, distorted negative thoughts associated with specific situations and maladaptive attitudes about depression. The therapist adopts an educational style, seeking the cooperation of the patients, so they can learn to recognise patterns of negative thinking and re-evaluate them. This approach requires the patient to practise their new skills between sessions through homework assignments and trying out new behaviours. Cognitive therapy usually consists of behavioural techniques; hence the name of cognitive-behavioural therapy (CBT). Moreover, CBT includes a wide range of interventions that share the basic theoretical assumption that the majority of human behaviour is learned and that cognitive activity determines behaviour.

CBT adopts a structured format, is limited in time and is based on the cognitive-behavioural model of affective disorders. It has been evaluated in a variety of contexts (primary care, specialised care and hospitalised patients), and is primarily compared with pharmacological treatment and using different patient samples[135.] The most frequent regime is 15-20 weekly sessions of about 50 minutes each, although there are also studies that adopt shorter formats (6-8 sessions); and it is assumed that the duration of the therapy may be prolonged in cases of greater severity or comorbidity.

CBT in group format is also used in patients with major depression. Group CBT is highly structured and has a strong psychoeducational component. It is usually organised into 12 x 2-hour sessions conducted over 8 weeks[13].

Mindfulness-based cognitive therapy (MBCT) is a variant of CBT in group format designed specifically for the prevention of relapse or recurrence. The usual format is 8 weekly group sessions of 2 hours duration, focusing on the detection and development of skills to cope with bodily sensations, thoughts and feelings associated with relapses[13].

Efficacy

In this section, the NICE guidelines[13] included 46 RCTs of cognitive behavioural therapy (individual CBT, group CBT and MBCT) compared against antidepressant drugs, other psychotherapy or the waiting list. They also evaluated the combination of individual CBT and antidepressants compared with the latter alone. Our subsequent update included 3 meta-analyses of individual CBT, 1 meta-analysis and 2 RCTs of group CBT and 4 RCTs focused on MBCT.

Individual CBT

The NICE guideline[13] included 16 RCTs evaluating the efficacy of CBT against different drugs in the treatment of major depression (mainly SSRIs and TCAs), by measuring the reduction of depressive symptoms through questionnaires. Most of the studies were conducted in patients with mild to moderate depression. The results for the BDI (Beck Depression Inventory) and HRSD (Hamilton Rating Scale for Depression) scales were not significantly different either at the end of the treatment or after 1 month of follow-up. However, no data on response or remission rates for the disorder were provided. At 12 months of treatment, 3 studies observed a certain superiority for CBT over antidepressants in BDI and HRSD depression scales, and an increased risk of discontinuation of the latter. One study also showed lower relapse rates for CBT than for drug treatment at 1 year. Two studies in patients with major depression[136, 137] found no differences between CBT and antidepressant drug treatment using BDI and Hamilton scale scores, both at the end of treatment and at 16 weeks. SR, 1+

Compared to other psychotherapies, the NICE guideline included 4 studies comparing CBT with interpersonal therapy (IPT) and found no clinically relevant differences in either the BDI scale or the HRSD at the end of treatment; suggesting that IPT could be as effective as CBT in treating depression. CBT and behavioural activation were compared in 3 studies and no clinically relevant differences at the end of treatment were found. Finally, 2 studies compared CBT with brief psychodynamic therapy and 1 with Gestalt therapy, although no definite conclusions could be drawn about their comparative efficacy[13].

When compared with patients on the waiting list, the NICE guideline included 4 low quality studies that demonstrated the effectiveness of CBT in both self-reporting and expert interview scales[13]. SR, 3

The NICE guideline[13] included 9 studies comparing the combined treatment of CBT + antidepressants with antidepressants only. The results showed that the combination treatment had less discontinuation risk than for antidepressants alone, as well as significantly reduced scores on both self-reporting and expert interview scales. However, the evidence for the efficacy of the combined treatment at 6-12 months was limited. In contrast to the above, the NICE guideline13 identified no benefit in adding antidepressant drug treatment to CBT, either at the end of the treatment or after 1 month of follow-up. SR, 1+

Our update included 3 meta-analyses conducted by the same first author, comparing CBT with "standard therapy", "non-intervention" and interpersonal therapy.

Jakobsen et al.[138] used the Cochrane systematic review methodology with meta-analysis and sequential analysis of randomised clinical trials to compare the effects of CBT with standard therapy (understood as any non-specific treatment) in major depressive disorder. Included were 8 trials (all at high risk of bias) that randomised 719 participants, all of them older than 17 years with a diagnosis of major depressive disorder. Four studies provided results using the HRSD and 4 with the BDI. The meta-analysis with data from the Hamilton scale showed that CBT significantly reduced depressive symptoms, when compared with standard therapy. However, for both fixed effects and random effects, the meta-analysis with the BDI data could not confirm the previous results. The authors suggested that CBT may not be an effective treatment for depressive disorder compared with standard therapy, and that more randomised trials with a low risk of bias, increased sample size and more clinically relevant outcome variables needed to be performed. However, it should be mentioned that there was a wide variability in these standard treatments.

Meta-analysis, 1+

Using the same methodology as above, Jakobsen et al.[139] compared the effects of CBT with "non-intervention" in major depressive disorder. There were 12 trials (all at high risk of bias) randomising a total of 669 participants, all aged over 17 years with a diagnosis of major depression. The meta-analysis with the Hamilton scale data showed that CBT significantly reduced depressive symptoms, when compared with no intervention, although the sequential analysis failed to confirm these results. Meanwhile, the meta-analysis of the BDI data also showed that CBT reduced depressive symptoms, with the sequential analysis confirming the results in this case. Few trials reported remission, suicidal ideation, suicidal behaviour and adverse effects, and no significant differences were found among the comparison groups. The authors suggested that CBT may be an effective treatment for major depression, although these results may be overestimated because of the possibility of systematic or random errors. Moreover, the effects of CBT on remission, suicide, adverse events and quality of life are unclear. For firmer conclusions, more randomised trials with a low risk of bias, longer monitoring periods evaluating the benefits or harm with clinically relevant outcome variables would be necessary.

Meta-analysis, 1+

Using the Cochrane systematic review methodology once again, Jakobsen et al.[140] compared cognitive behavioural therapy with interpersonal therapy in the treatment of major depressive disorder. There were 7 trials (all at high risk of bias) randomising a total of 741 participants. The meta-analysis of 4 studies using the Hamilton scale score at the end of treatment and the one with the BDI data found no significant difference between the two interventions. The sequential analysis of the trials showed that more studies are needed to confirm the existence of a differential effect. No trials reported on adverse effects.

Meta-analysis, 1+

Group CBT

Group CBT has less evidence and most of that is focused on mild to moderate depression. The NICE CPG included 4 studies that compared group CBT (via the Coping with Depression Programme) with the waiting list or standard therapy, and observed a significant reduction in depression scale scores at the end of treatment and at 6 months follow up. The NICE guidelines concluded that group format CBT could be an effective treatment for patients with mild depression[13]. SR, 1+

Feng et al.[141] performed a meta-analysis to determine the effect of group CBT on the level of depression and risk of relapse. They selected 32 RCTs with quality scores of 6-8 out of 10 (using the Cochrane Collaboration Guidelines), which compared group CBT with a control group (not specified, and without differentiating between active and non-active controls, such as a waiting list). After treatment, the group CBT was associated with a reduction in symptoms compared to the control group, although the meta-analysis showed significant heterogeneity between studies. At 6 months group CBT was again associated with a reduction in depressive symptoms compared with the control group. Beyond 6 months, group format CBT was not associated with a persistent effect of reduced symptoms, although it did have a low relapse rate. A subgroup analysis showed that the effect of group CBT was higher when compared with standard therapy rather than medication, if the session lasted about an hour compared to shorter sessions, if there were tasks to do at home and in patients with mild depression. The authors concluded that group format CBT had a moderate effect on the intensity of depressive symptoms up to 6 months and a small effect on the relapse rate when continued beyond 6 months. Meta-analysis, 1+

A placebo-controlled 10-week trial, randomised 368 patients with minor depression, dysthymia and mild to moderate depression, receiving sertraline (flexible doses up to 200 mg/day), group CBT (1 individual session and 9 group sessions of 90 minutes), guided self-help, sertraline or group CBT to patient choice or placebo. The superiority was seen for sertraline versus placebo and group CBT versus guided self-help (with the results of the latter being worse than any other treatment, including placebo)[142]. RCT, 1+

A RCT with a 5-year follow-up also found that brief group format cognitive therapy (8 weekly sessions of 2 hours) in patients in remission after a variety of treatments was more effective in preventing relapse than standard therapy[143]. RCT, 1+

Mindfulness-based cognitive therapy (MBCT)

The NICE guideline[13] included 2 RCTs assessing standard therapy in primary care against a combination of that treatment with psychotherapeutic intervention. The combined treatment showed significantly less risk of relapse and an increased risk of discontinuation. Another RCT compared MBCT with antidepressant treatment, with an average/moderate effect in reducing BDI and HRSD scale scores at 1 month and 15 month follow-up in favour of MBCT.

SR, 1+

Our update included 4 RCTs published in recent years on MBCT as a treatment for recurrent depressive disorder. Patients without a current depressive episode but with a history of at least 3 previous depressive episodes, treated with a combination of MBCT + standard therapy (which allowed antidepressant drugs) significantly reduced the rate of recurrence/relapse at 56 weeks when compared with the standard therapy group. Furthermore, the combined treatment group had an increased time to the first relapse compared with the control[144.] Patients in the MBCT group in another study of a similar design reported less depressive symptoms, anxiety and rumination and increased mindfulness skills compared with the standard therapy only group[145]. A group of 84 patients with remission criteria and at least 2 previous major depression episodes were randomised to continue antidepressant treatment (citalopram, sertraline, venlafaxine or mirtazapine), to replace it with 8 MBCT sessions or with placebo[146]. After the open phase of the trial, the patients were classified as in stable or unstable remission, depending on whether they maintained a HRSD score of < 7 at 5 months from the initial referral to randomisation, or if they had occasional elevations. There were no differences between treatments in relapse for the stable remission cases; while continuing with drug treatment or replacing with MBCT reduced the probability of relapse by 73% in the unstable cases. Finally, another study found that MBCT was superior to standard therapy in reducing reactivity to social stress, and the improvements were mediated by depressive symptoms[147].

Meta-analysis, 1+

7.2.2 Behavioural activation

Behavioural activation is a brief and structured therapy using different behavioural techniques to get depressed patients to learn to manage their life and change their environment to recover positive reinforcement[148,149].

The NICE CPG[13] included 7 RCTs comparing behavioural activation with alternatives. There were no clinically relevant differences between behavioural activation and CBT using BDI and HRSD scores at the end of treatment in 3 studies. Another study compared with placebo also found no significant differences in scale score reduction. When compared to other psychological interventions, 1 study compared behavioural activation with brief therapy, and noted an increased discontinuation risk in the second group. Another study compared it with supportive therapy and found better BDI scores at the end of the treatment for behavioural activation. A single study evaluated behavioural activation with antidepressant drug treatment. Although the evidence was limited, patients with moderate to severe depression and drug treatment had a lower risk of discontinuation with no significant differences in depression

scales. There were no differences between behavioural activation and antidepressants in terms of relapses per year of treatment.

Finally, a RCT conducted in patients with major depression adding behavioural activation therapy to antidepressant treatment was more effective than continuing with antidepressants alone, for both improvement in depressive symptoms and the levels of working and social functionality[150]. RCT, 1+

7.2.3 Problem-solving therapy

The association between depression and a deficit in solving social problems is widely recognized. Problem-solving therapy (PST) is a structured therapy limited in time, focusing on improving coping strategies and developing behaviour to deal with specific problems[13].

The NICE CPG[13] included 2 RCTs with PST. When compared with placebo, there was a significant reduction in depression scale scores, both self-administered and via expert interviews. However, there were no significant differences found when PST was compared with antidepressants or when the combination of PST and antidepressants was compared with the latter only. SR, 1+

No other study after the NICE guideline was found.

7.2.4 Couples therapy

The psychotherapeutic approach of including a partner is aimed at helping participants understand the importance of interaction with others in the development and maintenance of symptoms; thus trying to change the nature of these interactions to achieve relationships based on support and reducing the level of conflict[13]. Although it is not a specifically developed treatment for depression, some authors emphasise its indication for depression due to the influence that the partner may have on the initiation, maintenance or exacerbation and resolution of a depressive episode[13].

The NICE CPG[13] has 6 RCTs in its systematic review of couple therapy. Most of the studies followed the behavioural model although 2 of them were based on interpersonal therapy. Compared to the waiting list, 2 studies found that couple therapy significantly reduced self-administered depression scale scores at the end of treatment. When compared with CBT, 2 studies found no significant difference in the risk of discontinuation or the BDI and HRSD scale scores at the end of treatment or at 6 months. There were also 2 small sample size studies compared with IPT that gave wide confidence intervals and did not allow for conclusive results. SR, 1+

A study after the NICE guideline comparing couple therapy with the waiting list in women with major depression or dysthymia noted that this psychotherapeutic modality is an effective treatment for depression which improves psychological distress, the burden of depression and involvement in the process[151]. RCT, 1+

7.2.5 Interpersonal therapy

Interpersonal therapy was developed by Klerman and Weissman[152] as a treatment for depression, although its use has spread to other mental disorders. It focuses on current relationships and interpersonal processes and the goal is to reduce symptoms through resolving or coping with problem areas.

As discussed in the section on cognitive-behavioural therapies, NICE[13] included 4 studies comparing CBT with IPT without finding any clinically relevant differences in depression scale scores at the end of the treatment. Only one study compared IPT with placebo, and observed a lower risk of discontinuation and a significant reduction in expert interview scale scores at the end of treatment. When compared with standard therapy in primary care (including medication), 4 studies showed a significant effect for IPT on self-administered depression scale scores at the end of treatment, at 3 months and at 9 months follow-up. This effect was also seen in expert interview scale scores at 3 months and 9 months. In 1 study, the combination of IPT with antidepressants significantly reduced expert interview scale scores when compared with IPT alone. Another study of the combined treatment against antidepressants showed a significant effect on the expert interview depression scale scores at the end of treatment. Using the BDI and HRSD scores, 2 studies comparing IPT with antidepressant treatment found no significant differences between the groups at the end of treatment. SR, 1+

A RCT published after the NICE guideline evaluated the effect of treatment preferences on IPT efficacy and pharmacotherapy (escitalopram). It was revealed that the degree of preference for the treatment in both groups was related to the treatment efficacy[153]. RCT, 1+

7.2.6 Counselling

Counselling or psychological advice was initially developed by Carl Rogers[154,] but has now become a generic term that includes various interventions aimed at providing people with skills to enable them to explore, discover and find ways to wellbeing.

The NICE CPG[13] included 5 RCTs on counselling compared with antidepressants, standard therapy, CBT and different variants of the intervention. The evidence found is limited and based on patients with mild to moderate major depression. A study with some methodological limitations (differences in baseline characteristics of the participants) found no significant differences when comparing the effectiveness of counselling with antidepressants. Another study found no differences when comparing the combination of counselling and physician treatment in primary care with the latter only. Comparison with CBT was evaluated in 1 study, although the small sample size did not allow for conclusions about the relative effectiveness of the treatments. The first of 2 studies compared patient-centred counselling with emotion-focused counselling and found better BDI results for the latter; while the second compared the effectiveness of patient-centred counselling with in the process and found no significant differences. SR, 1+

No other study was found after the update

7.2.7 Short-term psychodynamic psychotherapy

Psychodynamic therapy is derived from the psychodynamic/psychoanalytic model, where the patient and therapist explore current and past conflicts of the patient, focus on their interpretation and work on them[13,155].

The NICE guideline13 included 6 studies of brief psychodynamic therapy. When compared with antidepressant drugs, the latter showed a significant reduction in expert interview depression scale scores at the end of treatment. However, another small sample size study showed no significant differences. One study found a high and significant risk of discontinuation in patients treated with brief psychodynamic therapy when compared with those treated with behavioural activation. When compared to the waiting list, 1 study showed a significant effect for psychodynamic therapy in expert interview scale scores. The same study also showed a similar effect when compared with supportive therapy. A follow-up study in patients with minor depression or dysthymia found that adding psychodynamic therapy to antidepressant treatment significantly reduced expert interview depression scale scores at 24 months and 48 months, when compared with drug treatment. Finally, another study compared the effectiveness of psychodynamic therapy in patients diagnosed with major depression with or without comorbid personality disorder, and observed more effectiveness in the latter case, although the small sample size did not allow for firm conclusions. SR, 1+

No other study was found after the update.

7.2.8 Other psychotherapeutic interventions

As part of the psychotherapeutic approach to depression, other less intensive interventions requiring less professional participation have been developed; these involve sessions of less frequency and duration, or with health professionals with lower levels of specialisation. Computerised cognitive behavioural therapy (CCBT) and guided self-help are usually included in this group of interventions[13,156].

In a directive issued by the NHS on improving access to psychological treatments, all these

treatments are grouped under the label of low intensity therapies and defined as "those employing less complex approaches than psychotherapy, in which the contact with patients is shorter and can be carried out by professionals with a lesser degree of specialisation, using non-traditional methods such as the telephone or the Internet"157. According to this definition, the intensity is defined by the following features: the complexity of the intervention, the duration of contact with professionals and their level of qualification and the intervention format[156]. Another definition of low intensity interventions emphasises their focus on increasing the volume of access to them[158].

This review includes studies in which CCBT and guided self-help were used as treatment for depression or its symptoms, although most of them were conducted with samples of patients with mild depression or depressive symptoms according to some scale (usually BDI). Many of them were conducted in the UK, in response to a recommendation from research by NICE, and with materials that have not to our knowledge been validated in Spanish (e.g. the Beating the Blues Programme, which consists of 8 weekly 50-minute sessions of CCBT).

Computerised cognitive behavioural therapy

CCBT is a structured intervention, similar in content to standard CBT, but implemented via a computer with a CD-ROM, DVD or an Internet connection (online CCBT)[13]. Contact with professionals usually occurs in the introduction to the programme, monitoring and at specific times if necessary.

The update of the NICE guideline included 7 RCTs comparing CCBT with group CBT, psychoeducation, waiting list, standard therapy and group discussion. Patients in these studies had mild to moderate symptoms of depression (BDI, 18-25), although only about half had a formal diagnosis of major depression. CBT was an effective treatment compared to the interventions evaluated, although the meta-analysis showed a moderate effect at the end of treatment. Evidence in the follow-up was limited, as only 2 of the studies assessed included a follow-up at 12 months and the effect size in these studies was small[13]. RCT, 1+

After the NICE CPG was issued, 4 RCTs were found evaluating the effectiveness of CCBT as a treatment for depression compared with other interventions, and 2 RCTs were found evaluating therapist-related variables on the efficacy of CBT.

A RCT conducted in primary care comparing online CCBT with the intervention of a therapist in real time (i.e. when the patients were online, they could contact the therapist) combined with standard therapy versus standard therapy only gave higher recovery rates at 4 and 8 months for the online patients. The sample consisted of patients diagnosed with depression according to ICD-10 and BDI scores over 14. All patients were diagnosed up to 4 weeks before starting the study and none had received prior psychotherapy or antidepressant treatment in the previous 3 months[159]. RCT, 1+

When compared with the waiting list, 2 forms of CCBT (based on guided self-help and therapy through email) achieved significant reductions in depression symptoms and gave very similar responses to each other[160]. RCT, 1+

Another RCT conducted in patients with major depression compared the effectiveness of CCBT therapy with online problem-solving therapy by the Internet and a waiting list group. Both therapies effectively reduced symptoms of depression, although the problem-solving therapy achieved a faster improvement than the CBT mode[161]. RCT, 1+

The effect of individualised CCBT was evaluated in one study by comparing it with online monitoring. The individualised Internet cognitive therapy (with content modified) was more effective than standard Internet CCBT treatment, especially in patients with more severe major depression according to DSM-IV and in the presence of comorbidity[162]. RCT, 1+

Another study found that both CCBT involving clinicians as well as that supervised by technicians had significant reductions in the symptoms of major depression, when measured by the BDI-II and PHQ-9 and compared with the waiting list[163]. RCT, 1+

Finally, a RCT compared CCBT with two types of self-help based on CBT. The results showed significant improvement in relation to the baseline for all three groups for both symptoms of depression and anxiety, although no significant differences between the various interventions were obtained[164]. RCT, 1+

Guided self-help

Guided self-help is an intervention using different materials designed to improve depression symptoms. The role of health staff is focused on guiding and evaluating the impact that reading this self-help material has on patients. For an intervention to be classified as guided self-help, it was considered that total contact with personnel throughout the intervention should not exceed 3 hours, or be limited to 3-6 occasions throughout the intervention. It can be done in individual, group or email support format[13].

The NICE guideline[13] included 16 RCTs of guided self-help. In general, these studies were found to be an effective intervention in people with subclinical symptoms of depression or mild major depression. No conclusive evidence in favour of self-help was found in 2 studies for long-term individual support when compared with a control group of waiting list patients and standard therapy. However, guided self-help of shorter duration was found to be more efficacious in reducing symptoms of depression when compared with the waiting list. Only 2 studies of a group format were included and there were insufficient data to draw definitive conclusions. There was evidence from 3 studies of self-help support via email for efficacy at the end of treatment, although a small size effect was observed at 6 months of follow-up[13]. SR, 1+

A subsequent RCT of short psychodynamic guided self-help via the Internet gave better results in improving depressive symptoms than an active control group (which received psychoeducation and Internet support)[165]. RCT, 1+

One study found a significant reduction in symptoms of depression for patients undergoing guided self-help on the Internet, both with and without contact with health staff, when compared with a waiting list group. The improvement was maintained at 6 months post-treatment. This study suggests that the effectiveness of self-help can be maintained without contact with healthcare staff[166]. RCT, 1+

A combination of guided self-help, relaxation and standard therapy significantly improved depressive symptoms and cognitive distortions, such as rumination and overgeneralisation, when measured with the HRSD. No differences were found between the 2 interventions (standard therapy + self-help vs. standard therapy + relaxation)[167]. RCT, 1+

Relapse Prevention

A recently published systematic review[156] aimed at evaluating the role of CCBT and guided self-help in relapse prevention took into account other short format interventions that required the intervention of a mental health specialist (less than 6 hours of contact with the patient). It included 14 published and 3 ongoing studies, of which 10 evaluated MBCT in the short format, while the rest were CBT-based interventions. The studies included, however, were very heterogeneous in methodology and found different results in terms of effectiveness for these interventions, so no firm conclusions could be drawn[156]. SR, 1+

A later RCT evaluated the effect of CCBT on the prevention of relapse in patients with major depression in partial remission and found that the relapse rate was lower in the CCBT group than in the control group (email contact with a therapist)[168]. RCT, 1+

Evidence summary

1+	CBT had a lower risk of early discontinuation of the treatment than antidepressant drug treatment, and lower rates of relapse at 1 year[13].
3	No differences were found between CBT and interpersonal therapy or behavioural activation at the end of treatment using HRSD and BDI scales. No definitive conclusions could be drawn about the relative effectiveness of CBT and brief psychodynamic therapy[13].

Cognitive-behavioural therapies	
1+	CBT had similar scores to antidepressant drug treatment (mainly SSRIs and TCAs) in the HRSD and BDI scales, both at the end of treatment and after 1 month of follow-up, while a certain superiority was observed for CBT at 12 months of treatment[13].
3	CBT was more effective in both self-reporting and expert interview scales when compared with patients on the waiting list[13].
1+	Combined treatment of CBT + antidepressants had a lower risk of discontinuation than antidepressants alone and significantly reduced scores on both self-reporting and expert interview scales. However, no benefit was observed in adding antidepressant treatment to CBT at the end of the treatment or after 1 month. The evidence of effectiveness of the combined treatment at 6-12 months is limited[13].
1+	A meta-analysis and sequential analysis of randomised clinical trials comparing the effects of CBT with standard therapy in major depression showed that CBT significantly reduced depressive symptoms when measured with the Hamilton scale, but not with the BDI[138].
1+	Another meta-analysis and sequential analysis of randomised clinical trials comparing the effects of CBT with no intervention in major depressive disorder showed that CBT significantly reduced depressive symptoms when measured by the Hamilton scale, although sequential analysis failed to confirm these results. A significant reduction was observed in the BDI scale scores, confirming the sequential analysis results[139].
1+	Another meta-analysis comparing CBT with IPT in the treatment of major depression found no differences in HRSD or BDI scale scores at the end of treatment. Sequential analysis of the trials showed that more studies are needed to confirm any differential effect[140].
1+	CBT in group format (*Coping with Depression Programme*) significantly reduced depression score scales at the end of treatment and at 6 months follow-up when compared to being on a waiting list or standard therapy[13].
1+	A meta-analysis found that group CBT was associated with a reduction in symptoms of depression at the end of treatment (with significant heterogeneity) and at 6 months when compared with the control group. Beyond 6 months, group format CBT was not associated with a persistent effect of reducing symptoms. However, it was associated with a low relapse rate[141].
1+	A controlled 10-week randomised trial was conducted of 368 patients with minor depression, dysthymia and mild to moderate major depression receiving sertraline, group CBT, guided self-help, sertraline or group CBT to patient choice or placebo. The overall effectiveness was measured by depression scales and showed the superiority of sertraline over placebo and group CBT over guided self-help[142].
1+	A RCT with a 5-year follow-up found that brief cognitive therapy in group format for patients in remission after a variety of treatments was more effective in preventing relapse than standard treatment[143].

1+	*Mindfulness-based cognitive therapy* (MBCT) combined with standard treatment by a Primary Care physician had a significantly lower risk of relapse and increased risk of discontinuation, compared with standard therapy[13].
1+	MBCT showed a medium to moderate effect in reducing depression scale scores at 1 month and 15 months of follow-up compared with pharmacological antidepressant treatment[13].
1+	The combination of MBCT + standard therapy (allowing antidepressants) in 2 RCTs significantly reduced the rate of recurrence/relapse at 56 weeks compared with a standard therapy group[144]. Patients also reported fewer depressive, anxiety and rumination symptoms and increased mindfulness skills compared to the standard therapy group alone[145]. Another study[146] showed that continuing with drug treatment or replacing with MBCT reduced the probability of relapse by 73%. Finally, MBCT was superior to standard therapy in reducing the reactivity to social stress, and improvements in emotional reactivity were mediated by depressive symptoms[147].
Behavioural activation	
1+	No clinically relevant differences in either self-reporting or expert interview depression scale scores were seen between behavioural activation and CBT or placebo at the end of treatment[13].
1+	Compared to brief therapy, behavioural activation has a lower risk of discontinuation and scored better scores than supportive therapy on the BDI scale at the end of treatment[13].
1+	No significant differences were found between behavioural activation and antidepressant treatment, discontinuation risk, depression scale scores or number of relapses for patients with moderate to severe depression after 1 year of treatment[13].
1+	Behavioural activation was more effective than standard therapy in primary care both in the improvement of depressive symptoms and levels of working and social functionality[150].
Problem-solving therapy	
1+	Problem solving therapy, compared with placebo, significantly reduced both self-reporting and expert interview depression scale scores. However, no significant differences were found when compared with antidepressants or when problem solving therapy in combination was compared with the latter alone[13].
Couples therapy	
1+	Compared to the waiting list, 2 studies found that couple therapy significantly reduced self- reporting depression scale scores at the end of treatment[13].
1+	Compared with CBT, 2 studies found no significant difference in the risk of discontinuation or in the depression scale scores at the end of treatment (BDI or HRSD) or at 6 months (BDI). The results compared with IPT were inconclusive[13].
1+	Compared to the waiting list, couple therapy for women with major depression or dysthymia improved psychological distress, the burden of depression and involvement in the process[151].

Interpersonal therapy	
1+	The NICE guide included 4 studies comparing CBT with IPT and found no clinically relevant differences in depression scale scores at the end of treatment[13].
1+	Only 1 study compared IPT with placebo, and had a lower risk of discontinuation and significant reduction in expert interview depression scales scores at the end of treatmen[t13].
1+	Compared with standard therapy in primary care (including medication), 4 studies showed IPT had a significant effect on self-reporting and expert interview scale scores at 3 and 9 months follow-up and on self-reporting scale scores at the end of treatment[13].
1+	No significant differences were found in BDI and HRSD scales at the end of treatment between IPT and antidepressant drug treatment groups in 2 studies[13].
1+	In 1 study, the combination of IPT with antidepressants significantly decreased expert interview scale scores when compared with IPT alone; while, in another, the combined treatment showed a significant effect over antidepressants only for expert interview depression scale scores at the end of treatment[13].
1+	A RCT conducted to evaluate the effect of treatment preferences on the efficacy of IPT and pharmacotherapy (escitalopram) showed that the degree of preference was related to the effectiveness of treatment for both groups[153].
Counselling	
1+	The evidence on counselling is limited and based on patients with mild to moderate major depression. A study with methodological limitations found no significant differences in effectiveness between counselling and antidepressants[13].
1+	Another study found no differences between the combination of counselling and primary care from a physician with the latter only[13].
1+	Counselling was compared with CBT in one study, but the small sample size did not allow for definitive conclusions about their relative effectiveness[13].
1+	Variants of the intervention were compared in 2 studies: the first compared patient-centred counselling with counselling focused on emotions, with the latter performing better. While the second compared patient-centred counselling with in the process, and found no significant differences[13].
Short-term psychodynamic psicotherapy	
1+	Brief psychodynamic therapy is less effective than antidepressant medication in reducing expert interview depression scale scores at the end of treatmen[t13].
1+	Compared with behavioural activation, brief psychodynamic therapy had a high and significant risk of discontinuation. While 1 study showed a significant effect on expert interview depression scale scores compared with the waiting list and a similar effect when compared with supportive therapy[13].

1+	For patients with minor depression or dysthymia, adding psychodynamic therapy to antidepressant treatment significantly reduced expert interview depression scale scores at 24 and 48 months follow-up, compared with drug treatment only[13].
1+	Psychodynamic therapy appeared to be more effective for patients diagnosed with major depression without comorbid personality disorder than with it, although the small sample size did not allow firm conclusions to be drawn[13].
Computerised cognitive behavioural therapy	
1+	There is evidence that CCBT is more effective in improving short-term depressive symptoms than group CBT, problem-solving therapy, standard therapy, psychoeducation, group discussion and the waiting list[13,159-161].
1+	CCBT had a similar effectiveness to problem-solving therapy in 1 study, although the latter obtained significantly faster improvement[161].
1+	Individual treatment with the therapist adapting the content is more effective than standard CCBT treatment, especially in patients with more severe depression and comorbidity[162].
1+	CCBT involving clinicians and that conducted by supervised technicians both obtained a significant reduction in depression symptoms compared with the waiting list[163].
1+	A study comparing CCBT with 2 different forms of CBT-based self-help showed significant improvement in both symptoms of depression and anxiety, although there were no significant differences between the different interventions[164].
Guided self-help	
1+	Guided self-help is an effective intervention for people with mild depression or subclinical symptoms of depression, although there is no evidence of long-term effectiveness[13].
1+	Guided self-help with short-term individual support is more effective than long-term and there is no conclusive evidence for guided self-help with support in a group format[13].
1+	One study suggested that the effectiveness of self-help can be maintained by contact with professionals or by no contact at 6 months after treatment[166].
1+	Guided self-help and relaxation with standard therapy for depression significantly improved depressive symptoms measured by HRSD and cognitive distortions. No differences between the 2 interventions (standard therapy + self-help vs. standard therapy + relaxation) were found[167].
1+	There is insufficient evidence on the effect of long-term low intensity psychosocial interventions or on relapse prevention[13,168].

Recommendations

√	The availability of psychotherapeutic treatment should be ensured for patients who need it.
B	In mild-moderate depression, a brief psychological treatment (such as cognitive behavioural therapy or problem-solving therapy) of 6-8 sessions over 10-12 weeks should be considered.
B	The psychological treatment of choice for moderate to severe depression is cognitive behavioural therapy or interpersonal therapy, of 16-20 sessions over 5 months.
B	Cognitive behavioural therapy should be considered for patients with inadequate response to other interventions or a prior history of relapses and/or residual symptoms.
C	Other psychological interventions should be considered when addressing comorbidity or the complexity of family or marital relationships, often associated with depression.
B	Patients with chronic and/or recurrent depression are recommended a combination of drug therapy and cognitive behavioural therapy.

7.3 Pharmacotherapy

Antidepressants are drugs aimed at improving symptoms associated with depression and there are different types according to their chemical structure and mechanism of action (Table 11). There is a latency in the onset of therapeutic effects which can be 2 to 4 weeks, although some studies show an earlier response, especially in patients who finally achieve remission of their symptoms[169].

Table 11. Classification of antidepressant drugs in Spain

Classic antidepressants	Non-selective MAOI	Tranylcypromine
	MAO-A selective MAOI	Moclobemide
	Heterocyclics	Tricyclics: Imipramine, Clomipramine, Trimipramine Amitriptyline, Nortriptyline, Doxepin Heterocyclics: Amoxapine, Mianserin, Maprotiline
New generation	SSRI	Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Escitalopram
	NDRI	Bupropion
	SNRI	Venlafaxine, Desvenlafaxine, Duloxetine
	SARI	Trazodone
	NaSSA	Mirtazapine
	NRI	Reboxetine
	Melatoninergic agonist	Agomelatine

Abbreviations - MAOI: Monoamine oxidase inhibitors; TCA: Tricyclic antidepressants (reuptake inhibitors of 5-HT and NA); SSRI: Selective serotonin reuptake inhibitors; NDRI: Norepinephrine-dopamine reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitors; SARI: Serotone antagonists and reuptake inhibitor (5-HT2 receptor and weak 5-HT uptake inhibitor); NaSSA: Noradrenergic and specific serotonergic antidepressant; NRI: Norepinaphrine reuptake inhibitor.

Source: Prepared by the authors.

The efficacy of drug treatment for major depression in adults is well documented, although there is controversy about which antidepressant is the most suitable. In general, the more severe the depression symptoms, the more benefit drug treatment provides.

7.3.1 Adverse effects and interactions profile

The classical or first generation antidepressants may have side effects poorly tolerated by patients and which interact significantly with other drugs or food. Thus, the new-generation antidepressants are nowadays the more prescribed[170]. Table 12 summarises the adverse effect profile of different antidepressants and Table 13 some specific effects and other special prescribing considerations. Finally, annex 3 shows the pharmaceutical form and costs of major antidepressants available in Spain.

The effects of a drug can be modified if taken with another due to the interaction of the pharmacodynamics of competition, enhancement or alteration in their physiological mechanisms. These interactions are easily predicted if the pharmacological properties of the different antidepressants are known (see Table 13)[171].

Pharmacokinetic interactions of antidepressants occur by inhibiting the hepatic cytochrome P450 enzymes involved in the metabolism of most psychotropic and non-psychotropic drugs. Thus, the inhibition of an enzyme specific to this system results in increased plasma levels (with possible toxicity) of those drugs metabolised by the enzyme. Fluvoxamine, fluoxetine and paroxetine have a high potential for inhibition of some isozymes in this system, while the effect of other antidepressants such as citalopram, mianserin, mirtazapine, reboxetine and venlafaxine is minimal[171].

As a general rule, it is recommended to choose antidepressants that interfere less with the metabolism of other drugs, especially in the case of polymedicated patients[172].

Table 12. Adverse effect profile of different antidepressants

		Central Nervous System				Anicholinergic		Cardiovas-cular	Gastrointestinal			Others				Overdose lethality
		Sedation	Insomnia	Headache	Termors	Dry mouth	Sweating	Hypoten-sion	Nau-sea	Diarr-hoea	Constipa-tion	Anxiety	Fatigue	Sexual Dysfunction	Weight gain	
TCA	Clomipramine	+	+	-	++	++		++	+			+	++	++	+	Moderate
	Amitriptyline, Dulosepin	++	-	-	+	++		++	-			-	-	+	++	High
	Imipramine	+	+	n/a	n/a	++		++	-			n/a	n/a	+	+	High
	Desipramine, Nortriptyline	+	+	-	-	+		+	-			+	-	+	-	High
	Lofepramine	-	+	n/a	n/a	+		+	-			n/a	n/a	?	-	Low
MAOI	Tranylcypromine	+	++	n/a	n/a	+		++	+			n/a	n/a	++	++/-	High
	Moclobemide	-	+	-	-	-		-	+			-	-	-	-	Low
SSRI	Citalopram	+	-	-	-	+	+	-	+	-	-	-	-	++	-	Low
	Escitalopram	-	-	-	-	-	-	-	+	-	-	-	-	+	+	n/a
	Fluoxetine	+	+	-	+	+	-	-	+	-	-	+	-	++	-	Low
	Fluvoxamine	++	-	++	+	+	+	+	++	-	+	++	-	++	-	Low
	Paroxetine	+	-	+	-	+	+	+	+	+	+	-	-	++	-	Low
	Sertraline	+	-	++	+	+	-	+	++	++	-	+	+	++	-	Low
NDRI	Bupropion	-	++	-	-	+	-	-	+	-	+	-	-	-	-	Moderate
SNRI	Venlafaxine	+	+	+	-	+	+	+	++	-	+	+	-	++	-	Moderate
	Desvenlafaxine	-	+	+	-	+	+	+	+	+	-	-	++	-	+	?
	Duloxetine	-	+	-	-	+	-	-	++	-	+	-	-	++	-	Moderate
SARI	Trazodone	++	-	-	-	+	-	+	-			-	+	-	+	Low
NaSSA	Mianserin	++	-			+		-	-					-	-	Low
	Mirtazapine	++	-	-	-	+	-	-	-	-	+	-	-	-	++	Low
NRI	Reboxetine	-	+		-	+		-	-					+	-	Low
MA	Agomelatine	-	-	+	-	-		-	-			+	-	-	-	?

These adverse events are for guidance only and based on information taken from several sources: primarily guidelines and datasheets.

Abbreviations: n/a = not available, MAOI monoamine oxidase inhibitors; TCA: Tricyclic antidepressants (5-HT and NA reuptake inhibitors); SSRI: Selective serotonin reuptake inhibitors; NDRI: Norepinephrine-dopamine reuptake inhibitors; SNRI: Serotonin-norepinephrine reuptake inhibitors; ASIR: 5-HT2 serotoninergic receptor antagonists and weak 5-HT uptake inhibitor; NaSSA: Noradrenergic and specific serotonergic antidepressant; NRI: Norepinaphrine reuptake inhibitor; MA: Melatoninergic agonist

++ Often; + Occasionally; - Rarely; ? Insufficient information.

Source: Prepared by authors and adapted from several sources[172-174].

Table 13. Specific features of main antidepressants and special prescribing considerations

Drug	Specific Features	Prescribing considerations
MAOI	Can cause insomnia, nervousness, hypertensive crisis (Tranylcypromine), sleep disturbances, nausea, agitation and confusion (Moclobemide	– Do not use tranylcypromine in combination with other antidepressant drugs. Generally, a period of 2 weeks is required after stopping taking MAOI and starting new antidepressants. If switching from an antidepressant to a MAOI, the waiting period is 1 week, but 5 weeks in the case of fluoxetine. – With moclobemide, interactions with tyramine are possible at high doses, but rare and mild. There are interactions with dextromethorphan/pethidine (excitation/depression). Avoid clomipramine, levodopa, sympathomimetic agents and SSRIs. Caution with fentanyl, morphine and tricyclics. With cimetidine, halve the dose of moclobemide
TCA	Potential arrhythmogenic effect. Orthostatic hypotension.	– CKD: Amitriptyline, clomipramine, imipramine and trimipramine do not require dose adjustment. – LF: Avoid in liver failure (hepatic metabolism and high protein binding). – Avoid in epilepsy. – Avoid recent AMI or conduction abnormalities, ECG should be performed before starting the treatment, especially in people with cardiovascular risk factors. – Tricyclic antidepressants, such as amitriptyline, imipramine and nortriptyline, have lower known risks during pregnancy than other antidepressants; although they have greater toxicity/lethality in overdoses than SSRIs – Not suitable during breastfeeding. – Pharmacodynamic interactions: sedative pharmaceuticals, drugs, alcohol; anticholinergics (antihistamines or antipsychotics); antihypertensives; drugs that alter cardiac conduction (antiarrhythmics), and electrolyte balance (diuretics); anticonvulsants; serotonergic drugs (serotonin syndrome).

SSRIs as group	Gastrointestinal bleeding risk, especially in older patients, or if taken with NSAIDs. All SSRIs (and SNRIs) have been associated with transient nausea and gastrointestinal discomfort when starting or increasing the dose. It is advisable to start medication with half the usual dose, and gradually finish it with half the usual dose, except for fluoxetine.	– CKD: If mild or moderate, citalopram, escitalopram, paroxetine and sertraline do not require dose adjustment. If severe, take lower doses and increase more slowly. – Good treatment choice for epilepsy. No clear difference between them. – They do not seem to have teratogenic effects, although there have been some cases of malformations. When used from the 20th week of pregnancy, may be associated with increased risk of persistent pulmonary hypertension in the newborn. – Pharmacodynamic interactions: Other serotonergic drugs (serotonin syndrome); aspirin and NSAIDs.
Citalopram	May increase QT interval	– CKD: Low risk in patients with mild to moderate CKD. Dose reduction in severe CKD. – LF: Low risk in patients with liver disease. – Avoid or care required in arrhythmia. – Maximum dose of 20mg in patients over 65 years.
Escitalopram	May increase QT interval	– CKD: Low risk in patients with mild to moderate CKD. Dose reduction in severe CKD. – LF: Low risk in patients with liver disease. – Avoid or care required in arrhythmia. – Maximum dose of 10mg in patients over 65 years.
Fluoxetine	Anorectic and weight loss effect. Has the longest half-life.	– Severe CKD: reduce dose or take on alternate days. – LF: Avoid or adjust dose in liver disease due to its hepatic metabolism and long half-life. – Good cardiac safety. – Fluoxetine is the SSRI with the lowest known risk during pregnancy, so it would be a treatment option in this case.
Paroxetine	Possible weight gain. Possible withdrawal symptoms; gradual reduction is advised.	– CKD: Low risk in patients with mild to moderate CKD. Dose reduction in severe CKD. – LF. Low risk in patients with liver disease. – Good cardiac safety. – Administration during the first 3 months of pregnancy may be associated with cardiac malformations. – It is advisable to avoid in pregnancy. – May be used if breastfeeding.
Sertraline	Greater incidence of diarrhoea than with other SSRIs. Possible withdrawal symptoms; tapering is advised	– CKD: Low risk in patients with mild to moderate CKD Dose reduction in severe CKD. – Very good cardiac safety. – Could be used if breastfeeding if expected benefits outweigh potential risks to the child.

Bupropion	Caution in all situations that reduce the seizure threshold. Does not produce sedation. Can make insomnia worse. May be advantageous for depressed patients with Parkinson's disease due to its dopaminergic action. Less sexual dysfunction.	– CKD: In renal failure, 50% dose reduction. – LF: Reduced dose in liver disease. – Avoid or care required in arrhythmia. – Avoid in epilepsy and in patients with agitation. – Increased dose dependent on diastolic blood pressure
Venlafaxine	Potential increase in diastolic blood pressure and heart rate, dose dependent. Potential arrhythmogenic effects (long QT, tachycardia). Reduced seizure threshold. Risk of gastrointestinal bleeding. Possible withdrawal symptoms, tapering advised.	– CKD: Reduce dose by 25-50% if mild to moderate; 50% if severe and avoid use of sustained release formulation. – LF: Dose reduction to 50% in liver disease. – Avoid or care required in arrhythmia. – Caution in epilepsy. – Do not use in patients with uncontrolled glaucoma.
Desvenlafaxine	As for venlafaxine: possible withdrawal symptoms; tapering advised. Risk of bleeding.	– CKD: If moderate: do not increase dose above 50 mg/day. If severe: 50mg every other day. – LF: No adjustment required. Doses greater than 100 mg/day not recommended.
Duloxetine	Potential increase in diastolic blood pressure (less frequent than venlafaxine). Possible withdrawal symptoms; tapering advised. Risk of bleeding.	– CKD: No adjustment needed if mild to moderate. – LF: Avoid if possible, due to reduced clearance, even if liver damage is mild. Liver damage and isolated cases of fulminant hepatic failure have been reported. – Caution in epilepsy. – Caution in heart disease. – Caution in patients with known bleeding diathesis. – Do not use in patients with uncontrolled glaucoma.
Trazodone	High sedative effect. Orthostatic hypotension. Less sexual dysfunction. Possible priapism.	– Do not use in recent AMI. – Used in low doses with SSRIs for the treatment of insomnia. – Caution with arrhythmias.
Mirtazapine	Increased appetite and weight gain. Oedema. Less sexual dysfunction.	– CKD: Caution if moderate due to 75% renal excretion. – LF: It is metabolised via the liver, so a dose reduction of 50% is recommended. – Good cardiac safety. – Caution in epilepsy

Reboxetine	No specific features.	– CKD: Increases its half-life. – LF: Although it does not seem to be associated with hepatotoxicity, it is recommended to start with 50% of the dose. – Use with caution in epilepsy.
Agomelatine	Contraindicated in liver disease. Do not use in p over 75 years. Less sexual dysfunction. Improved sleep quality.	– CKD: Caution if moderate to severe. – LF: Contraindicated with any degree of hepatic impairment. Serum transaminase control required. – No significant cardiovascular effects.

Abbreviations: TCA: tricyclic antidepressants; SSRI: Selective serotonin reuptake inhibitors; NSAID: Nonsteroidal anti-inflammatory drugs; CKD: Chronic kidney disease; LF: Liver failure.

Source: Compiled by the authors and adapted from various sources[171,175,176].

7.3.2 Safety and efficacy of antidepressant drugs

Key question

- What is the safety and efficacy of antidepressant drugs in the treatment of depressive episodes in adults?

Some of the studies evaluating the efficacy/effectiveness and safety of the pharmacological treatment of depression have a number of limitations that could compromise their internal or external validity:

– In general, a relatively small number of patients are involved in the studies and for a limited period. Patient selection is very strict, and usually excluding those with comorbidity. In addition, monitoring is very strict and under controlled conditions, which limits the generalisability of the results for clinical practice.

– Certain infrequent adverse effects can be observed only when a large number of people have used a drug for an extended period.

– For a comparator drug, the compared doses are not always the ones most appropriate, nor the supposedly equipotent.

– Because they are funded studies, in many cases by the manufacturer itself, there are potential conflicts of interest.

– Sometimes there is bias in publishing the scientific data obtained from a study, depending on the nature and direction of the results.

– Some of the differences in efficacy between first and second generation antidepressants are partly related to methodological issues, as there have been improvements in the design and quality of studies over the past three decades that have resulted in smaller differences, especially compared to the placebo.

– The use of samples with a larger number of subjects, but more heterogeneous from a clinical perspective, may also explain the difficulty in finding differences in efficacy between antidepressants and checking minor differences from the placebo.

– Treatment response and remission are evaluated only by scores from scales such as the HRSD or BDI which, although they are instruments with adequate psychometric properties, are far from optimal as the only variable to evaluate the efficacy of a drug.

7.3.2.1 Efficacy and safety of tricyclic antidepressants

The mechanism of action of tricyclic antidepressants (TCAs) or first-generation antidepressants is by inhibiting the reuptake of serotonin and noradrenaline. Although all TCAs block the reuptake of both monoamines, some are more selective than others; e.g. clomipramine is more serotonergic and imipramine more noradrenergic. All TCAs cause anticholinergic side effects to different degrees (dry mouth, blurred vision, constipation, urinary retention and sweating), sedation and postural hypotension, so it is necessary to start with low doses and gradually increase them[13].

To address the safety and efficacy of TCAs in the treatment of major depression, a search was performed in clinical practice guidelines, systematic reviews, meta-analyses and primary studies, with a selection of items specifically for these drugs.

The CPG which included a larger number of TCA studies was prepared by NICE[13]. In this section, the authors verified the lack of substantial new evidence since the original guideline was published in 2004. Other later systematic reviews also included no new studies[177,178].

Tricyclic antidepressants versus placebo

The CPG prepared by NICE[13] included 108 RCTs comparing the following TCAs against placebo: imipramine (66 studies), amitriptyline (30 studies), dosulepin (4 studies), nortriptyline (4 studies) and clomipramine (3 studies). In all cases, the TCAs were more effective than placebo, with similar results for each drug. However, participants taking TCAs were more likely to leave treatment early due to side effects. SR, 1+

Undurraga et al.[177] analysed 39 RCTs conducted with TCAs, of which 35 had already been included in the NICE CPG[13.] The authors conducted a meta-analysis reporting on the difference in the response obtained for each drug versus placebo, and amitriptyline was ranked first in efficacy (measured as response rate). The authors also compared the efficacy of different types of antidepressants with tricyclics showing superiority to placebo when compared with other groups of antidepressants and against them en masse. SR, 1+

Recently, von Wolff et al.[178] conducted a systematic review to examine the efficacy and acceptability of SSRIs and TCAs in the treatment of patients with chronic major depression, dysthymia, double depression or recurrent depression without complete remission between episodes. They evaluated the response to treatment and abandonment due to side effects in 20 RCTs of which 19 were mostly of patients with dysthymia. None of these studies were included in the NICE[13] or Undurraga[177] reviews. TCAs were superior to placebo in both response and remission, yielding a NNT of 4 for response and 7 for remission, although with significantly higher rates of patients with adverse effects than placebo. SR, 1+

Tricyclic antidepressants versus other antidepressants

Although amitriptyline was not the first TCA, nor the best tolerated or most prescribed, it is the standard medication against which newer antidepressants are compared for efficacy and tolerability. This is why NICE established two subsections: one evaluating amitriptyline and the other including any other TCA as comparator

NICE[13] included 48 studies reporting on the tolerability of amitriptyline and its efficacy, published between 1977 and 1999. The study period was between 3 to 10 weeks (mean = 5.71 weeks) and they were carried out in different scenarios. From the available data, amitriptyline was compared with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine, dothiepin/dosulepin, doxepin, imipramine, lofepramine, minaprine, nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine. No clinically relevant differences were observed between amitriptyline and any other antidepressant after evaluating the response rate. However, patients treated with other antidepressants had fewer side effects and were less likely to leave the study. SR, 1+

In the other tricyclic antidepressants section, NICE[13] included 94 studies on: clomipramine, doxepin, desipramine, imipramine, dothiepin/dosulepin, nortriptyline, amineptine and lofepramine. The studies reported tolerability and efficacy and were carried out in different scenarios. In 11 studies, over 80% of participants were older than 65 years. No clinically relevant differences were observed between TCAs and other antidepressants in the response rate, remission or in the probability of reducing the depression symptoms at the end of treatment as measured by the HRSD and MADRS. Some favourable clinically relevant differences were found for treatment acceptability and tolerability for other antidepressants over TCAs, due to a reduced probability of leaving the study early due to side effects. SR, 1+

The systematic review prepared by von Wolff et al.[178] found no differences between TCAs and SSRIs, either in response rate or remission. However, SSRIs showed statistically significant lower dropout rates and adverse effects than TCAs. SR, 1+

Evidence summary

Tricyclic antidepressants versus placebo	
1+	Tricyclic antidepressants are more effective than placebo in both response and remission, but are more likely to cause side effects and early treatment dropout[13,178].
1+	When compared with placebo, tricyclic antidepressants show greater efficacy than each of the different groups of antidepressants and as a group[177].
1+	Of all tricyclic antidepressants, amitriptyline has the highest efficacy compared to placebo, followed by imipramine[177].
Tricyclic antidepressants versus other antidepressants	
1+	No clinically relevant differences between amitriptyline and other antidepressants (including SSRIs) were found after evaluating the response rate. However, patients treated with other antidepressants had fewer side effects and were less likely to leave the study[13].

1+	There were no clinically relevant differences in the response or remission rates for tricyclic antidepressants (other than amitriptyline) when compared with other antidepressants; although there were significant differences in favour of other antidepressants on reducing the probability of leaving the study early due to side effects[13].
1+	Another systematic review found no differences between tricyclic antidepressants and SSRIs, either in response rate or remission. However, SSRIs had lower dropout rates and adverse effects than tricyclics[178].

7.3.2.2 Efficacy and safety of monoamine oxidase inhibitors

Selective monoamine oxidase inhibitors (MAOIs) exert their therapeutic effect by reversibly or irreversibly binding to monoamine oxidase, the enzyme responsible for the catabolism of noradrenaline and serotonin. All MAOIs have the potential to induce a hypertensive crisis if foods containing tyramine (also metabolised by monoamine oxidase) or prescribed drugs that increase monoaminergic neurotransmission are ingested. Reversible inhibitors of monoamine oxidase (RIMA), such as moclobemide, have much less chance of causing a hypertensive crisis and dietary restrictions are not usually necessary. These restrictions, potentially serious drug interactions and the availability of safer antidepressants have led to the prescription of irreversible MAOIs being uncommon, even in hospitalised patients. However, MAOIs are still cited as the most effective in treating atypical depression[13]. The only 2 MAOI antidepressants currently available in Spain are moclobemide and tranylcypromine.

The NICE CPG[13] was updated to address the efficacy and safety of MAOIs in the treatment of major depression by evaluating moclobemide and phenelzine and, as with tricyclic antidepressants, the authors used the 2004 guideline edition literature search due to the lack of new evidence. Because phenelzine is not sold in Spain, it was removed from this section. On the contrary, a review of selegiline was included, although it is not approved for the treatment of depression in Spain and sometimes is used as compassionate use.

Moclobemide

It is a reversible inhibitor of monoamine oxidase A, in contrast to traditional MAOIs which irreversibly inhibit both MAOs. Therefore, it does not require any dietary restrictions, and the drug interactions that can lead to a hypertensive crisis are less significant, with a shorter washout period needed when wanting to switch to another antidepressant. It is generally well tolerated, with few anticholinergic effects.

NICE included 26 RCTs reporting on drug tolerability and efficacy. There were 16 studies comparing moclobemide with TCAs, 8 with SSRIs and 7 with placebo. No participant had atypical features of depression and the dose received was between 150 and 600mg. All the studies included were published between 1984 and 1998, had a study period of between 4 and 7 weeks and were conducted in different areas. In 1 study, participants were older than 65 years. From the available data, it was possible to compare moclobemide with amitriptyline, fluoxetine, fluvoxamine, dothiepin/dosulepin, clomipramine, imipramine, nortriptyline and placebo[13]. Moclobemide was significant clinically more favourable than placebo in the response rate and in reducing depression symptoms at the end of treatment. However, there were no clinically relevant differences between moclobemide and placebo on reducing the probability of early treatment discontinuation for any reason or due to side effects[13]. Compared with other antidepressants (TCAs and SSRIs), moclobemide showed no clinically relevant differences in response rate or remission. Moclobemide was more likely than other antidepressants to reduce treatment discontinuation due to side effects and especially when compared with TCAs[13]. SR, 1+

Selegiline

Selegiline is a MAOI that selectively inhibits MAO B, responsible for the breakdown of dopamine. It is indicated for Parkinson's disease as monotherapy in the early stages or as an adjunct to levodopa. In Spain, the indication for the treatment of depression is not approved.

Undurraga et al.[177] conducted a systematic review from 1980 to 2011 of those controlled trials assessing the efficacy of antidepressant drugs in major depression. Of the MAOIs, phenelzine[1,] tranylcypromine1 and selegiline[3] were evaluated. The authors conducted a meta-analysis on the comparative efficacy of each drug against placebo, and selegiline obtained a response rate of 33% above placebo (relative risk 1.33). SR, 1+

Evidence summary

MAOIs versus placebo	
1+	A clinically relevant difference was observed in favour of moclobemide for both response rate and reducing depression symptoms at the end of treatment. There were no clinically relevant differences between moclobemide and placebo on reducing the likelihood of early discontinuation of treatment[13].
1+	Selegiline has shown a response rate 33% higher than placebo[177].
MAOIs versus other antidepressants	
1+	Moclobemide showed no clinically relevant differences in response or remission rate over other antidepressants (TCAs and SSRIs)[13].
1+	There was less probability of treatment drop-out with moclobemide due to the side effects of SSRIs and especially TCAs[13].

7.3.2.3 Efficacy and safety of SSRIs and other new generation antidepressants

SSRIs and the rest of the new generation of antidepressants are a heterogeneous group of drugs that act on the neurotransmitters serotonin, noradrenaline and dopamine. Although the efficacy of both the first and new generation antidepressants is very similar, the first generation tend to have poorly tolerated side effects and an increased risk of lethality in overdose and drug interactions. As a result, the role of the newer antidepressants in the treatment of major depression is crucial.

Comparison between SSRIs

There have been numerous RCTs performed to compare the efficacy of different SSRIs with each other.

The systematic review by the *Agency for Healthcare Research and Quality* (*AHRQ*)[170,179] included 34 studies in which all possible comparisons between different SSRIs were evaluated, with the exception of citalopram vs escitalopram and paroxetine vs fluvoxamine, about which no studies were included. There were some significant differences found in the meta-analysis, although of questionable clinical relevance as shown by the following comparisons: SR, 1+

- Escitalopram vs citalopram: There were 5 published studies comparing these 2 drugs included, with 1802 patients and an OR favourable towards escitalopram. The NNT to gain an additional response at 8 weeks with escitalopram compared to citalopram was 13. However, taking into account the efficacy of escitalopram and citalopram compared to the other SSRI antidepressants and others, no significant differences were found in the response rate in the analysis of mixed comparisons.

- Sertraline vs fluoxetine: There were 4 studies involving 940 patients; the response OR was favourable towards sertraline and the NNT to gain an additional response at 6-12 weeks of treatment with sertraline was 13.

Following this AHRQ meta-analysis, a RCT was performed comparing the efficacy of escitalopram vs citalopram at 6 weeks in patients with major depression; with no differences in the two groups being found for response or remission rates[180]. RCT 1+

The results from 3 trials showed no significant differences among the SSRIs in the response for maintenance (relapse prevention) or remission (prevention of relapse or recurrence) for the following antidepressants: escitalopram vs paroxetine, fluoxetine vs sertraline and fluvoxamine vs sertraline[170,179]. RCT 1+

Comparison between SSRIs and other second generation antidepressants

Overall, the 46 included RCTs found no significant differences between the efficacy of SSRIs and other second-generation antidepressants (NDRI, SNRI, SARI and NaSSA)[170,179]. The only statistically significant difference was fluoxetine being more favourable than venlafaxine, although this was of doubtful clinical relevance. RCT 1+

Although it did not result in a greater efficacy, mirtazapine had a faster onset of action in 7 studies than other SSRIs (citalopram, fluoxetine, paroxetine and sertraline). The NNT for an additional response after 1 or 2 weeks of treatment was 7, which was similar to the response rates at 4 weeks[170, 179]. RCT 1+

After the AHRQ meta-analysis, 3 RCTs were published which again found no significant differences between SSRIs and other antidepressants:

- SSRIs (fluoxetine, paroxetine, citalopram and sertraline) vs venlafaxine extended release (XR): an open multicentre design RCT with 1,385 patients compared the efficacy of different SSRIs against venlafaxine XR. The remission rates were similar in both groups at 25 weeks of treatment, although some secondary variables (*Clinical Global Impression and Quick Inventory of Depressive Symptomatology-Self-Report*) were favourable towards venlafaxine XR. There was a 49% drop-out overall, but the reasons for were similar in both groups[181]. RCT 1+

- SSRIs (citalopram, fluoxetine, paroxetine and sertraline) vs duloxetine: an open design RCT comparing duloxetine with 4 generic SSRIs chosen by the physician. The primary efficacy variable was the *Quick Inventory of Depressive Symptomatology-Self-Report* which found no significant differences in the remission rate in both groups at 12 weeks[182]. RCT 1+

- Paroxetine vs bupropion: a RCT of 74 patients with major depression at high risk of suicide evaluated the efficacy of the antidepressants in reducing suicidal ideation and behaviour. The secondary endpoint employed was the HRSD-17 (total score without the suicidal ideation item). No differences in suicidal behaviour or severity of depression were found, although the patients with greater levels of suicidal ideation at baseline and treated with paroxetine obtained a significant improvement in this variable compared to those treated with bupropion[183]. RCT 1+

There were 2 RCTs that compared escitalopram with desvenlafaxine and fluoxetine with venlafaxine which found no significant differences for preventing relapse or recurrence[170,179]. Furthermore, a nonrandomised study revealed that rates of rehospitalisation were similar in patients that continued treatment with fluoxetine or venlafaxine[170,179]. SR 1+

Comparison between other second generation antidepressants

There are fewer publications for this section. Specifically, the AHRQ review included 8 RCTs comparing duloxetine with desvenlafaxine, mirtazapine with desvenlafaxine, mirtazapine with trazodone, venlafaxine with bupropion and bupropion with trazodone. Overall, no significant differences in response rates for the treatment of acute major depression were found[170,179]. SR 1+

A RCT comparing trazodone with venlafaxine also found no significant differences in preventing relapse or recurrence[170,179]. RCT 1+

Desvenlafaxine

Desvenlafaxine is a recently approved and marketed antidepressant in Spain[184]. As with venlafaxine, it is a potent serotonin and noradrenaline reuptake inhibitor and a weak dopamine reuptake inhibitor. The AHRQ systematic review included 3 RCTs comparing desvenlafaxine with duloxetine for treating the acute phase of major depression, and escitalopram vs placebo for relapse prevention. The meta-analysis concluded that the efficacy of desvenlafaxine was similar to that of other second-generation antidepressants[170,179]. The studies included are described below:

When comparing desvenlafaxine (50 and 100 mg/day) with duloxetine (60 mg/day), no significant differences in response or remission rates were found at 8 weeks of treatment[185]. RCT 1+

A RCT comparing desvenlafaxine (100-200 mg/day) with escitalopram (10-20 mg/day) for the prevention of relapse in postmenopausal women with major depression found that the relapse rates at 6 months were similar in the two groups[186]. RCT 1+

Desvenlafaxine had statistically significantly better results for rate of and time to relapse compared with placebo[187]. RCT 1+

Safety and acceptability of SSRIs and other second generation antidepressants

In general, the dropout rates were similar for SSRIs and other second generation antidepressants[170,172,179]. The AHRQ meta-analysis studied the dropout rates due to adverse events and lack of efficacy separately. The first were similar between SSRIs and bupropion, mirtazapine and trazodone; however, duloxetine showed a 67% increase in dropout for this reason and venlafaxine 40%. For withdrawal due to lack of efficacy, the SSRIs had similar rates to bupropion, mirtazapine and trazodone, whereas venlafaxine had 34% less risk of abandonment than the SSRI drug group[170,179]. SR 1+

Approximately 63% of patients on SSRIs or other second generation antidepressants had an adverse event during the treatment. The most common were diarrhoea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremor and weight gain[170,179]. SSRIs had a higher rate of gastrointestinal side effects than other second generation antidepressants, although duloxetine and venlafaxine were specifically higher for nausea and vomiting than SSRIs. Mirtazapine and trazodone had high sedation rates[170,173,179]. SR 1+

In general, the severity of adverse events was similar for individual antidepressants, although their frequency was different for some of them[170,179]. This information was consistent with results from observational studies: SR 1+

- Venlafaxine led to a 52% increase in the incidence of vomiting compared with other SSRIs.
- Mirtazapine produced a greater weight gain than the other second generation antidepressants of 1-3kg after 6-8 weeks of treatment.
- Sertraline led to rates of diarrhoea 8% higher than other antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine and venlafaxine).
- Trazodone led to an increase of 16% in sleepiness, compared with bupropion, fluoxetine, mirtazapine, paroxetine and venlafaxine.

An observational study in Spain found that 59% of patients treated with second generation antidepressants experienced sexual dysfunction[170,179]. In addition, 7 RCTs found that bupropion caused lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine and sertraline (NNT 7). Paroxetine caused higher sexual dysfunction rates than other second generation antidepressants (16% vs 6%)[170,179].

SR of different studies 1+, 3

SSRIs and second generation antidepressants do not appear to be associated with an increased risk of suicide[170,172,179] and there was no evidence of any differences between the various antidepressants[170,179].

SR of different studies 1+, 3

New generation antidepressants have sometimes been linked with suicidal ideation and behaviour, mainly in childhood and adolescence. The problem lies in that antidepressant RCTs in children and adolescents do not usually consider suicide as an outcome variable. The most common study is for suicidal behaviour to be assessed retrospectively, once it is has occurred, which makes it difficult to link any variables that could be directly related to suicidal ideation or behaviour. In fact, the attribution to antidepressants of a role in the increased risk of suicide is contradictory to studies published to date. To reach a conclusion of this nature, one would have to remove all biological, psychological and social factors associated with suicide, as it is a multifactorial fact not attributable to one isolated or specific cause[51,188].

CPG 4

Despite the importance of serious adverse events such as seizures, cardiovascular events, hyponatraemia, hepatotoxicity and serotonin syndrome, there is no conclusive evidence of their frequency[170,179].

SR 1+

Evidence summary

1+	Some statistically significant differences are observed in the efficacy of SSRI antidepressants when compared with each other but they are of dubious clinical relevance[170,179]. No significant differences in maintaining response or achieving remission are seen for different SSRIs (escitalopram vs paroxetine, fluoxetine vs sertraline and fluvoxamine vs sertraline)[170,179].
1+	No significant differences were observed in the efficacy of SSRIs and other second generation antidepressants (NDRI SNRI, SARI and NaSSA)[170,179].
1+	Although some studies have shown that mirtazapine could be more rapidly acting than other SSRIs (citalopram, fluoxetine, paroxetine and sertraline), its antidepressant efficacy is no greater. The response rate at 4 weeks is similar, and the NNT is 7 for an additional response in the first or second week[170,179].
1+	Comparison between different SSRIs and venlafaxine XR showed no difference in remission rates, although some secondary endpoints were favourable to venlafaxine XR[181].
1+	No differences were found in efficacy between SSRIs and duloxetine[182].
1+	For patients with major depression and a high risk of suicide, no differences were found between paroxetine and bupropion in suicidal behaviour or severity of depression; although patients with higher levels of suicidal ideation at baseline and treated with paroxetine obtained a significant improvement compared to those treated with bupropion[183].

1+	The comparison between second generation antidepressants (duloxetine vs desvenlafaxine, mirtazapine vs desvenlafaxine, mirtazapine vs trazodone, venlafaxine vs bupropion and bupropion vs trazodone) showed no significant differences in the response rate, nor for preventing relapse or recurrence between trazodone and venlafaxine[170,179].
1+	No differences were observed in response or remission rates between desvenlafaxine and duloxetine[185], nor for relapse rates between desvenlafaxine and escitalopram[186].
1+	Approximately 63% of patients treated with second generation antidepressants have mild adverse events during treatment (diarrhoea, dizziness, dry mouth, fatigue, headache, nausea, sexual dysfunction, sweating, tremors or weight gain). Overall comparisons between individual antidepressants showed no differences in the intensity of adverse events, although their frequency was different among some antidepressants[170,172,173,179].
3	An observational study conducted in Spain found 59% of patients treated with second generation antidepressants had sexual dysfunction[170,179].
1+	Bupropion leads to lower rates of sexual dysfunction than escitalopram, fluoxetine, paroxetine and sertraline; while rates of paroxetine are higher than other second generation antidepressants[170,179].
1+	SSRIs and second generation antidepressants do not appear to be associated with an increased risk of suicide in adults[170,172,179].

7.3.2.4 Efficacy and safety of reboxetine

It is a relatively selective noradrenaline reuptake inhibitor, and can produce side effects such as insomnia, dizziness, dry mouth, constipation and a reduction in serum potassium levels.

The AHRQ report did not include reboxetine in its review, so a search was performed in clinical practice guidelines, systematic reviews and primary studies by selecting items specifically for this drug. The documents recovered were the NICE CPG on depression[13] and 2 systematic reviews prepared by the Institute for Quality and Efficiency in Health Care (IQWiG)[189,190] and by Cipriani et al.[191]. Subsequently, a literature search of randomised clinical trials was performed to complete the above searches, which yielded only the Wiles et al. randomised clinical trial[192].

Reboxetine versus placebo

The NICE CPG[13] included 3 RCTs comparing reboxetine with placebo. There was strong evidence that reboxetine had a better response rate (3 studies, n = 479) and some evidence regarding the remission rate (1 study, n = 254) when compared with placebo. The evidence was insufficient to establish any clinically relevant difference between reboxetine and placebo in any measure of acceptability or tolerability.	SR 1+

The IQWiG[189,190] conducted a systematic review and meta-analysis to evaluate the efficacy and safety of reboxetine versus placebo or SSRIs in the treatment of major depression. All randomised, double-blind clinical trials published up to February 2009 were included, as well as unpublished ones conducted by the manufacturer. There were 8 trials comparing reboxetine and placebo: 2 were published in the NICE guide and the rest were unpublished. The authors found no statistically significant difference between reboxetine and placebo for remission at the end of treatment. They observed a great heterogeneity in the response rate but, after excluding one study, there were was no statistically significant difference between reboxetine and placebo. The authors also noted that hospitalised patients were more likely to have a good response compared with outpatients. Finally, reboxetine was associated with higher rates of adverse events and drop-outs for this reason than placebo. SR 1+

Reboxetine versus other antidepressants

The NICE CPG[13] included 3 RCTs comparing reboxetine with TCAs and 2 with SSRIs. No clinically relevant differences between reboxetine and the other antidepressants were observed at the end of treatment in rates of response or remission or in reducing depression symptoms. The evidence regarding acceptability and tolerability of treatment was insufficient to clinically assess for any relevant differences between reboxetine and other antidepressants in reducing the likelihood of early treatment discontinuation for any reason or due to side effects. SR 1+

The IQWiG systematic review[189,190] noted that the remission rate for reboxetine was significantly less than that for SSRIs and similar, although not significantly less when compared to individual SSRIs (fluoxetine, paroxetine and citalopram). However, reboxetine was inferior to paroxetine and inferior to citalopram when evaluating remission with the MADRS depression scale in the long-term. Finally, there was no difference between reboxetine and SSRIs, including when these were analysed individually, in the number of patients with at least one adverse event. SR 1+

Cipriani et al.[191] systematically reviewed 117 RCTs conducted between 1991 and 2007, which compared 12 second generation antidepressants, including reboxetine, for the treatment of unipolar major depression in adults by intention to treat analysis. In this meta-analysis, reboxetine was significantly less effective than other antidepressants and less well tolerated than 5 of them (bupropion, citalopram, escitalopram, fluoxetine and sertraline). Reboxetine was also less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline. SR 1+

The RCT conducted by Wiles et al.[192] randomised 601 outpatients with ICD-10 criteria for a depressive episode and 15 or more points on the *Beck Depression Inventory* (BDI) scale receiving either a SSRI (citalopram, 20mg daily) or reboxetine (4mg twice daily); 91% of the patients were followed to 6 months. The authors concluded that treatment with reboxetine does not confer any advantage over SSRIs in patients with major depression in primary care. RCT 1+

Evidence summary

Reboxitine versus placebo	
1+	A clinically relevant difference was found in 3 RCTs for reboxetine over placebo for response rate with some evidence only regarding remission rate[13].
1+	A subsequent systematic review of published and unpublished RCTs found no statistically significant differences between reboxetine and placebo for response or remission rate at the end of treatment[189,190].
1+	Reboxetine was associated with higher rates of adverse effects and drop-outs than placebo[189,190].
Reboxitine versus other antidepressants	
1+	No clinically relevant differences were found in 3 RCTs between reboxetine and other antidepressants for response or remission rates or in reducing depression symptoms at the end of treatment[13].
1+	Reboxetine had a remission rate significantly lower than SSRIs in 1 systematic review[189,190].
1+	A meta-analysis found that reboxetine was significantly less effective than 11 antidepressants[191], and 1 RCT showed that treatment with reboxetine did not confer any advantage over in patients with major depression in primary care[192].
1+	No differences in adverse events were found between reboxetine and other antidepressants, such as SSRIs[13,189,190], and it was worse tolerated than bupropion, citalopram, escitalopram, fluoxetine and sertraline individually[191].

7.3.2.5 Efficacy and safety of agomelatine

This is an antidepressant with a different mechanism of action, as it is a melatonin receptor (MT1 and MT2) agonist and serotonin 5-HT2C receptor antagonist. It has no affinity for α or β adrenergics, histaminergics, cholinergics, dopaminergics or benzodiazepines[193]. It gained EMEA approval in 2009 as a treatment for major depression in adults, although associated with a risk management plan due to possibility of liver damage. It is pending approval by the FDA. In Spain, it is approved for the treatment of major depressive episodes in adults with a recommended dose of 25 mg/day, which can be increased to 50 mg/day.

The NICE major depression guideline[13] did not include agomelatine in its drug therapy review as it was not licensed in the UK at that time. Meanwhile, it is an antidepressant of choice[173] in the Canadian guideline because of its adverse event profile.

Efficacy versus placebo

In a meta-analysis of 5 RCTs[194-198] conducted by Singh et al.[199], agomelatine (n = 1274) at doses of 25, 35 and 50mg was superior to placebo (n = 689) in the acute phase treatment of major depression. However, after excluding a RCT involving patients in the depressive phase of bipolar disorder[195] from the analysis, the dose of 25mg was no longer significantly better than placebo. A subgroup analysis found that younger patients responded better to agomelatine compared to placebo than those patients with previous or shorter episodes.	Meta-analysis 1+

Subsequently, Koesters et al.[200] conducted a systematic review of all published and unpublished trials, of short and long term duration, assessing the efficacy of agomelatine compared to placebo in the treatment of major depression. It included 13 studies, 7 of which had not been published[201-207]. Ten studies evaluated the results in the short term[194-198,202-206] and 3 in the long-term[201,207,208]. All studies had more than 100 patients per arm, were funded by the manufacturer and (except for 1 study[204]) all contributed scores with the HRSD scale. The short-term studies (2,947 patients) showed that treatment with agomelatine was associated with a statistically significant improvement of -1.51 points on the HRSD scale over placebo, although this difference may not be clinically relevant. The difference in the scores was -2.12 for the published studies, -0.73 for the unpublished studies, thus the difference between both was -1.39 (p = 0.02). When analysing the risk of relapse, long-term studies (983 patients) showed no significant effect over placebo. The authors emphasise the magnitude of the publication bias, as none of the negative studies was published. In addition, the size of the effect on the published studies was 3 times higher than on the unpublished.

Meta-analysis 1+

There is only 1 published RCT comparing the efficacy of continued treatment with agomelatine for relapse prevention with placebo. The comparison was made after 24 weeks (after a test period of 8-10 weeks of open treatment with agomelatine) and a significantly lower relapse rate was found in the group receiving agomelatine (measured with the HRSD scale) than placebo, including the group of patients with severe depression[209].

RCT 1+

Efficacy versus other antidepressants

The previous meta-analysis by Singh et al.[199] also evaluated agomelatine (n = 834) with other antidepressants (n = 864) [fluoxetine[210], paroxetine[195,] sertraline[211] and venlafaxine[212,213]], and found a certain superiority for agomelatine in antidepressant efficacy. However, it is questionable whether the magnitude of the effect is clinically relevant and whether the features of the sample are applicable to the general population.

Meta-analysis 1+

Another meta-analysis[214] found significantly improved efficacy for agomelatine versus other antidepressants in both the total HRSD-17 scale score and response rates for patients with both moderate and severe depression. As well as the 3 RCTs included in the previous meta-analysis[210,211,213], this meta-analysis included a new study evaluated against escitalopram[215] and 2 unpublished studies (compared with escitalopram and paroxetine).

Meta-analysis 1+

The comparative efficacy studies and their main parameters included in both meta-analyses are summarised in Table 14. In all cases, the response and/or remission rates were not significantly different from the active comparator, although a significant decrease for the group receiving agomelatine[211] was found in one study.

Table 14. Published agomelatine studies: Comparative efficacy parameters and results

Study	Variables (primary/ secondary)	Comparison	No	Duration (weeks)	Dose (mg/ day)	% Response	% Remission
Loo[1]	HRSD/MADRS, CGI	Paroxetine	711	8	1/5/25 vs 20	62/51/61 vs 56; P= n/a	21/18/30 vs 26, P= n/a
Lemoine 2007[1,2]	Sleep quality HRSD17, CGI	Venlafaxine	334	6	25-50 vs 75-150	76 vs 71; P=NS	n/a
Kennedy 2008[1]	Sexual function MADRS, CGI	Venlafaxine XR	276	12	50 vs 150	82 vs 80; P=NS	73 vs 70; P=NS
Kasper 2010[1,2]	Sleep-wake cycle HRSD17, CGI	Sertraline	307	6	25-50 vs 50-100	70 vs 61; P=NS	33 vs 29; P=NS
Hale 2010[1,2]	HRSD17, CGI	Fluoxetine	515	8	25-50 vs 20-40	72 vs 64; P=NS	32 vs 28; P=NS
Quera Salva 2011[2]	Polysomnographic HRSD17, CGI	Escitalopram	138	24	25-50 vs 10-20	77 vs 74; P=NS	48 vs 42; P=NS

ND = Not available, NS = Not significant. Responses and remission rates were measured by the HRSD-17 or Montgomery-Asberg Depression Rating Scale (MADRS).

[1] Included in Sigh et al.

[2] Included in Kasper et al.

Source: Prepared by the authors

The main objective of 1 RCT, not included in the previous meta-analyses, was to compare agomelatine (25-50 mg/day, n = 30) with venlafaxine (75-150 mg/day, n = 30) for anhedonia in patients with major depression. Antidepressant efficacy (HRSD), anxiety and overall clinical improvement were measured as secondary variables. At 8 weeks, agomelatine had similar scores for depression and anxiety, although it was significantly better for reducing anhedonia216. However, a limitation of this study was the lack of prior evidence for venlafaxine being used specifically to treat anhedonia. RCT 1+

Finally, Laux et al.[217] conducted a prospective observational study (VIVALDI) on 3,317 patients diagnosed with major depression as the first manifestation (36%) or as a recurrent episode (64%). Patients were eligible only if the decision to start treatment with agomelatine (25-50 mg/day) had been taken before inclusion in the study. Comorbidity (mainly anxiety or panic disorder) was seen in 38% and associated somatic diseases seen in 54%. The assessment of depressive symptoms was performed at 12 weeks in all patients and in the subgroups of major depression (56.7%) and over-65s (13.5%). As a group, the decrease in patients' MADRS score was 18.3 points, with a 65.8% response rate (48.4% early response) and 54.8% remission. About 80% of patients improved with regard to sleeping difficulties and night-time awakenings, thus improving their daytime sleepiness. Adverse effects were about 10%. Case series 3

Safety and acceptability: Adverse effects profile

A review that included 1,120 patients treated with agomelatine (25-50 mg/day), 998 patients with placebo, 284 patients with fluoxetine (20 mg/day) and 283 patients with paroxetine (20 mg/day) found that the percentage of adverse effects was similar for agomelatine (53%), placebo (52%) and fluoxetine (49%), but higher for paroxetine (68%). The most common adverse effects of agomelatine, although present in less than 15% of patients were, in order of incidence: headache, nausea, dizziness, dry mouth, diarrhoea, drowsiness, fatigue, abdominal pain and anxiety. These adverse effects were slightly higher for the dose of 50 mg/day than 25 mg/day, but were generally mild or moderate. The only significantly different adverse effects of agomelatine were dizziness, numbness and blurred vision, when compared with placebo[218]. — SR 1+

The percentage of long-term adverse effects (34 weeks) were similar for agomelatine (39%) and placebo (38%), although slightly less than fluoxetine (32%) and higher for paroxetine (45%). The most frequent adverse effects were headache, back pain and insomnia, although these were present in less than 10% of patients. The only adverse effect significantly higher than the placebo was insomnia. As with short-term adverse effects, they were more frequent with a dose of 50 mg/day than 25 mg/day[218]. — SR 1+

In both meta-analyses included in the efficacy section[199,214], losses due to adverse effects were significantly lower in the group treated with agomelatine than with comparators. — Meta-analysis 1+

Sexual dysfunction

Agomelatine, bupropion, mirtazapine and moclobemide show similar percentages of sexual dysfunction to placebo[173]. — SR 1+

No significant differences between agomelatine and venlafaxine were found in 1 RCT evaluating sexual function as a primary endpoint[212]. — RCT 1+

Sleep

Patients treated with agomelatine significantly improved in subjective sleep quality, compared with venlafaxine[213]. — RCT 1+

Differences in sleep effectiveness and latency measured by actigraphy were found in favour of agomelatine compared with sertraline, although no significant differences were found in the amplitude of the sleep-wake rhythm[211]. — RCT 1+

Agomelatine was associated with reduced REM sleep latency, while preserving the number of sleep cycles, compared with escitalopram. In addition, evaluation with visual analogue scales indicated that treatment with agomelatine reduced daytime sleepiness[215]. — RCT 1+

Discontinuation symptoms

A RCT[219] studied the abrupt discontinuation in patients who received 12 weeks of treatment with agomelatine (25 mg/day) or paroxetine (20 mg/day). There were no discontinuation symptoms in the group receiving agomelatine in either the first or second week after discontinuation. Meanwhile, the discontinuation symptoms after the first week, but not the second, for the group receiving paroxetine were significantly higher than in the agomelatine group.

RCT 1+

Liver function

There is a risk of elevated transaminases in patients treated with agomelatine. Triple the normal values were found in 1.4% of patients taking a dose of 50 mg/day, in 1% of those on a dose of 25 mg/day and 0.7% with placebo. Although some cases were described of elevated transaminases not associated with signs of liver damage and severe hepatic reactions (10 times the normal limit), these were reported less frequently[218]. It is currently contraindicated with any degree of hepatic impairment and requires serum transaminase evaluation.

SR 1+

As a result, the Spanish Agency of Medicines and Medical Devices (AEMPS)[220] recommended that liver function be monitored in the following situations:

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- At the start of treatment with agomelatine.
- At 3 weeks, 6 weeks (end of acute phase), 12 weeks and 24 weeks (end of maintenance phase), and periodically thereafter.
- When the dose of agomelatine is increased at the same frequency as the start of treatment.
- When clinically indicated.
- Any patient with increased serum transaminases should have repeat liver function tests within 48 hours.
- Treatment should be discontinued immediately if the increase in serum transaminases is over 3 times the normal upper limit, or if patients have symptoms or signs suggestive of possible liver damage (dark urine, acholia, jaundice, right upper quadrant pain or sudden unexplained and prolonged fatigue).
- Caution is recommended when prescribing agomelatine to patients with already elevated transaminase levels or those who have risk factors for liver damage (being overweight or obese, non-alcoholic hepatic steatosis, considerable alcohol consumption, concomitant use of other potentially hepatotoxic drugs or diabetes).

Evidence summary

1+	Agomelatine is more effective than placebo in the treatment of moderate to severe major depression, both in the acute phase[199] and for relapse prevention[209].
1+	Younger patients and those with a greater number of previous episodes and of a shorter duration respond more favourably to agomelatine than placebo[199].
1+	Agomelatine is more efficacious than other active comparators (paroxetine, venlafaxine, venlafaxine XR, sertraline, fluoxetine and escitalopram)[199,214], although the size of the effect brings the clinical relevance of these results into question[199].
1+	Agomelatine was more efficacious than venlafaxine in reducing anhedonia in 1 RCT, though not in reducing the symptoms of depression or anxiety[216].
3	A prospective observational study of 3,317 patients diagnosed with major depression and treated with agomelatine showed a decrease in the MADRS scale score of 18.3 points at 12 weeks, with a 65.8% response rate and 54.8% remission. About 80% of patients improved in difficulty of falling asleep and nocturnal awakenings, as well as daytime sleepiness[217].
1+	The most common adverse effects of agomelatine are present in less than 15% of patients and are slightly higher with a dose of 50 mg/day than 25 mg/day[218].
1+	The losses due to adverse effects in clinical trials were significantly lower in the groups treated with agomelatine than with the comparators[199,214].
1+	Agomelatine, bupropion, mirtazapine, moclobemide and transdermal selegiline show similar percentages of sexual dysfunction to placebo[173].
1+	A RCT that evaluated the effect of agomelatine found no significant differences with venlafaxine for sexual function[212].
1+	Agomelatine was more efficacious than venlafaxine, sertraline and escitalopram for different sleep-related parameters[211,213,215].
1+	In a study evaluating discontinuation symptoms for agomelatine and paroxetine, none were found in either the first or second week after discontinuation with agomelatine, while there were discontinuation symptoms in the first week for a group receiving paroxetine[219].
1+	Patients treated with agomelatine had a risk of increased transaminase (1.4% at doses of 50 mg/day and 1% with 25 mg/day). Severe hepatic reactions (10 times the normal limit) were reported less frequently[218].
4	The AEMPS recommended liver function monitoring at 3, 6, 12 and 24 weeks, and periodically thereafter, after starting agomelatine treatment, when the dose of agomelatine is increased and when clinically indicated[220].

7.3.2.6 Role of benzodiazepines in the treatment of depression

Benzodiazepines are effective as anxiolytics and hypnotic drugs and have a rapid onset of action. Despite having no specific antidepressant effect, they can produce improvement in some symptoms of depression. However, they are associated with tolerance, dependence and withdrawal symptoms that can occur after 4-6 weeks of continuous use. To avoid this problem, they are recommended to be used for no more than 2-3 weeks[13].

Expert opinion 4

Evidence summary

4	Benzodiazepines can produce improvement in some symptoms of depression. However, they should not be used for more than 2-3 weeks to prevent the development of dependence[13].

7.3.3 Treatment dose and duration to prevent relapse

Key question

- How long and at what dose should drug treatment be maintained after remission of depressive symptoms?

The risk of relapse and recurrence in major depression is high, so it is important to establish how long drug treatment should be maintained after recovery from an episode. Different RCTs and meta-analyses have shown that maintaining drug therapy effectively prevents recurrence of depressive symptoms, but have not found predictors of risk of relapse[221,222]. In general, patients discontinuing antidepressant therapy are at increased risk of recurrence than those who continue[221.] However, the longer the treatment lasts, the less the difference in the risk of recurrence in treated patients and controls; i.e. the benefit of prolonging treatment decreases with time. Therefore, adjusting the treatment time length after recovery is an important challenge for each patient[223,224].

NICE recommends maintaining antidepressant medication treatment for at least 6 months after remission of the episode[13]. Other guidelines recommend a period of 12 months after achieving remission of a first depressive episode[225].	SR 3
The maintenance dose should be the same as that which that obtained the improvement, as it has been observed that patients who have the dose reduced have higher relapse rates than those who continue with the same dosage[226].	Meta-analysis 1+

It is difficult to make specific recommendations on long-term antidepressant treatment, so it is preferable to perform a personalised approach for each patient and carefully evaluate the benefits (prevention of relapse/recurrence) and the risks of administering a drug long-term (e.g. side effects and financial cost).

The NICE guideline proposed more than 6 months maintenance depending on the number of previous depression episodes, the presence of residual symptoms or the occurrence of comorbidity or psychosocial difficulties[13].	SR 3
The Canadian guideline[227] considered that patients with risk factors (Table 15) require long-term antidepressant treatment for a minimum of 2 years and sometimes for life[221,222]. Although there is no empirical evidence, long-term maintenance treatment could also be considered in patients with risk factors for vulnerability to depression, such as early onset, when there are adverse psychosocial factors or chronic diseases[227].	SR 3

Table 15. Risk factors for long-term maintenance of antidepressant treatment

– Advanced Age
– Recurrent (3 or more) episodes
– Chronicity or associated psychotic symptoms
– Severe episodes or difficulty in treating them
– Significant comorbidity (mental or physical)
– Residual symptoms (lack of remission) during the current episode
– History of recurrence after stopping antidepressant treatment

Source: Lam et al.[173].

It is important to verify compliance with the medication according to an appropriate time and dose. A study carried out in Spain monitoring compliance with medication over a period of 3 years found that only 22% of the evaluated patients managed to maintain treatment for the recommended period, i.e. a minimum of 6 months. The majority of 78% discontinued treatment before reaching that deadline, with the highest percentage of abandonment during the first four months. It was also observed that men were more likely than women to abandon the drug treatment early; with 50% of men reported to have stopped medication after 2 months and 50% of women after 3 months[228].

Case Series 3

Antidepressant withdrawal symptoms

Discontinuation of antidepressant treatment may be associated with withdrawal symptoms, characterised by symptoms such as irritability, nausea, insomnia, gait instability, sweating and paresthesia.

There have been reports of such reactions after either an abrupt halt or a gradual decrease of the drug with almost all antidepressants, including: selective reuptake inhibitors (SSRIs), tricyclic antidepressants, anti-monoamine oxidase (MAO) inhibitors, and others like venlafaxine, mirtazapine, trazodone and duloxetine.

Among SSRIs, which is a relatively homogeneous group of drugs, differences in pharmacokinetics, such as half-life of elimination or metabolism, may be the most clinically relevant parameters (Table 16). Thus, withdrawal symptoms are more common in patients who discontinue drugs with a relatively short half-life, such as paroxetine, than in those with longer half-lives, such as fluoxetine[229].

Thus, antidepressant treatment should be stopped by reducing the dose gradually, usually over a period of 4 weeks, although some people need longer periods, particularly with drugs with a short half-life such as paroxetine or venlafaxine. Because of its long half-life, a gradual reduction with fluoxetine would not be necessary[13].

Expert opinion, 4

Table 16. Average life and metabolism of the major antidepressants

	SSRI						New Antidepressants					MAOI		Tricyclic Antidepressants					
	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Paroxetine CR	Sertraline	Duloxetine	Mirtazapine	Trazodone	Venlafaxine	Venlafaxine XR	Moclobemide	Tranylcypromine	Amitriptyline,	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline
Half-life (hours)	35	27-32	84-144	21	15-20	26	11-16	20-40	7	3-13	3-13	1-2	2-4	9-25	22-84	14-25	11-23	10-16	18-35
Active metabolite	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No

Source: Warner et al. (2009)[229]

Evidence summary

3	The NICE CPG recommends maintaining treatment with antidepressant medication for at least 6 months after remission of the episode. The need for more than 6 months maintenance would depend on the number of previous episodes of depression, the presence of residual symptoms or the occurrence of comorbidity or psychosocial difficulties[13].
3	Other CPGs recommend maintaining treatment with antidepressant drugs 12 months after remission of the episode, and considering long-term (a minimum of 2 years) antidepressant treatment for those patients with risk factors[225].
1+	The maintenance dose should be the same as that given during improvement, as it has been observed that patients who reduce the dose have higher relapse rates than those who continue with the same dosage[226].
3	A study conducted in Spain found that only 22% of patients were able to maintain treatment during the recommended period (a minimum of 6 months); meanwhile, 78% discontinued treatment before reaching that deadline, with the highest percentage of abandonment occurring during the first 4 months. It was also observed that men were more likely than women to abandon the drug treatment early; with 50% of men reportedly stopping medication after 2 months and 50% of women after 3 months[228].
4	Antidepressant treatment should be stopped by reducing the dose gradually; usually over a period of 4 weeks, although some people need longer periods, particularly with drugs with a short half-life such as paroxetine or venlafaxine. Because of its long half-life, a gradual reduction would not be necessary with fluoxetine[13].

Recommendations

√	Before starting antidepressant treatment, patients must be adequately informed of the expected benefits, side effects and possible delay in the therapeutic effect.
A	The initial selection of drug therapy should be based mainly on the side effect profile and tolerability, safety and pharmacological properties, as well as other factors such as previous response to treatment, cost and patient preferences.
A	SSRIs are antidepressants with the most evidence and better risk/benefit ratio, and should be considered as the first choice of treatment.

√	All patients with moderate depression treated with drugs should be re-assessed within 15 days of the treatment start, and within 8 days in the case of severe depression.
D[GPC]	Benzodiazepine treatment may be considered for patients with anxiety, insomnia and/or agitation, although they should not be used for longer than 2-3 weeks to prevent the development of dependence.
√	Patients undergoing drug therapy must be closely monitored, at least for the first 4 weeks.
D	Antidepressant treatment should be maintained for at least 6 months after remission of the episode, and aspects such as previous episodes, comorbidity and the presence of other risk factors should be evaluated before deciding on withdrawal of treatment.
A	It is recommended that maintenance treatment be performed with the same dose at which the response was achieved.
D[GPC]	To avoid withdrawal symptoms, the antidepressant treatment dose should be reduced gradually, usually over a period of 4 weeks; particularly for drugs with short half-lives like paroxetine or venlafaxine.
D[GPC]	If withdrawal symptoms occur, a diagnostic confirmation should be performed and, if the symptoms are significant, reintroducing the original antidepressant at effective doses should be considered (or the use of another antidepressant in the same class with a long half-life) and the dose gradually reduced.
Q	When drug treatment is prescribed, the patient's perception should be explored and a positive attitude will be favoured. In addition, adequate monitoring for side effects, as well as evolution of the symptoms and functional capacity, should be performed. Moreover, after obtaining patient authorisation, any doubts the family has about the treatment must be clarified to gain their support.

8. Strategies for resistant depression

Despite progress in the treatment of affective disorders, one of the biggest problems in its management in clinical practice is the lack of or incomplete response to treatment. Another drawback is that there is no universally accepted definition of the concept of resistance to treatment in the scientific literature, which complicates the interpretation of the findings of the various studies and making evidence-based recommendations.

The 2004 NICE guideline considered resistant depression as that not responding after 2 drug treatments of an adequate dose and time. This definition was also proposed by the STAR*D study (*Sequenced Treatment Alternatives to Relieve Depression*) from the *US National Institute of Mental Health's* (NIMH), which showed that after 2 therapeutic trials without response, the probability of remission decreased considerably. However, the NICE 2009 update[13] moved away from this concept of resistance, mainly because it believed the definition to be arbitrary, not supported by evidence and perceived as a pejorative term by both clinicians and patients. It therefore proposed to consider the treatment of depression not responding as a higher level in the stepwise treatment model (see Figure 1) rather than a classification based solely on the non-response of patients. Other clinical practice guidelines, such as the Canadian or the British Association of Psychopharmacology, have also adopted a similar approach, based on addressing the lack of response, regardless of the number of previous single failed attempts[172,173].

Following these earlier proposals, this guideline considers resistant depression as that which partially or does not respond to drug treatment. The degree of the resistance, and therefore the strategy to follow, will depend on factors such as treatment response in both previous and current episodes, the presence of risk factors and the profile and severity of symptoms.

There are different strategies for dealing with resistant depression. Among the nonpharmacologic methods are psychotherapy (usually in combination with drug treatment) and electroconvulsive therapy. Pharmacological strategies can be grouped into the following categories: increasing the dose, changing to another antidepressant and a combination of antidepressants and enhancement with another pharmacological agent[230].

8.1 Psychotherapeutic strategies in resistant depression

Key question

- What is the role of psychotherapy as an enhancement or alternative in patients with resistant depression?

The effectiveness of psychotherapy as a treatment for depression not responding to treatment has been investigated less than pharmacological strategies. Existing studies are mainly based on cognitive behavioural therapy, so the comparative effectiveness of different psychotherapeutic interventions is unknown at present.

Trivedi et al.[231] conducted a systematic review of RCTs in which the clinical utility of psychotherapy (cognitive behavioural or interpersonal) was evaluated for the management of resistant depression, defined as partial or no remission after 6 weeks of drug therapy of an adequate dose. The authors included 7 studies in which psychotherapy was used as an enhancement

in 5 and as a replacement in 2. However, one of these RCTs[232] was rejected as it was a pilot study of small sample size identified in the review update.

Two of the RCTs included belonged to the multicentre STAR*D study, and examined the role of cognitive therapy and pharmacological strategies as enhancement or replacement for citalopram, given in a 14-week initial treatment for resistant depression (HRSD ≥14). The study design allowed patients to refuse any treatment strategy before randomisation, so that less than a third agreed with true randomisation. This resulted in asymmetric sample sizes for the treatment arms and inadequate statistical power to detect any small or moderate effects of the cognitive therapy in the arms. Although this could have negatively affected the internal validity, the applicability was improved after taking patient preference into account.

In the STAR*D study[233] enhancement arm, 180 patients with inadequate response to initial citalopram treatment received enhancement with cognitive therapy (n = 65) or drug treatment (n = 117). The first group received 16 sessions of CBT over 12 weeks and continued with citalopram, while the second group enhanced citalopram with bupropion or buspirone. After treatment, no significant differences were found in percentage remission or in the mean QIDS-SR scale scores between the two groups. RCT 1+

In the substitution arm of the same study[233], patients changed citalopram for 16 sessions of CBT over 12 weeks (n = 36) or treatment with bupropion, sertraline or venlafaxine (n = 86). As in the empowerment arm, both treatment groups had a similar rate of remission, and equal mean scores on the QIDS-SR scale. RCT 1+

The effect of enhancement with CBT was analysed in another study after no improvement with drug therapy[234]. In this study, 158 patients were randomised to receive cognitive therapy plus standard treatment or standard treatment alone. The CBT was provided in 16 sessions over 20 weeks, with 2 booster sessions, while the standard therapy consisted of a 30-minute appointment with a psychiatrist every 4 weeks and continuation of the prior drug treatment. While participants in both groups improved, the post-treatment analyses showed no significant differences in scores on the HRSD or BDI scale. The lack of homogeneity of the patients included in this study represented a methodological limitation to consider. RCT 1+

Patients with resistant depression (defined as residual symptoms after an adequate antidepressant treatment for at least 6 weeks) receiving dialectical behaviour therapy (DBT) were compared in a small sample size study[235] with those on the waiting list for this treatment. The patients in the intervention group received 16 x 90-minute sessions every week of group coping techniques. They were able to maintain the pharmacological treatment and continue with individual psychotherapy, as long as it was not cognitive therapy. The patients on the waiting list continued with their standard therapy. After treatment, better HRSD or BDI scale scores were observed in the DBT group. The study quality was limited by the small sample size and the confounding factor of allowing patients to continue with individual psychotherapy. RCT 1-

In another RCT[236], 44 patients with resistant depression (defined as HRSD scores between 8 and 15 after 8-14 weeks of treatment with antidepressants) enhanced treatment with 12 sessions of cognitive therapy or lithium. The CBT group patients were reassessed every 4 weeks and the lithium group, every 2. After treatment, lower HRSD scale scores were observed in the group treated with lithium, although there were no significant differences in BDI scale scores. One limitation of this study was that it included only patients with partial response to initial antidepressant treatment (HRSD between 8 and 15) and excluded those without response (HRSD ≥ 16). Another limitation was the lack of sufficient statistical power to detect clinically important differences, due to the necessary sample size for this not being calculated initially. RCT 1+

A low-quality RCT[237] evaluated the efficacy of CBT as a replacement strategy in 37 patients with resistant depression (although this was not specifically defined, patients continued to have depressive symptoms after 16 weeks of drug treatment). The patients were randomised to receive cognitive therapy (27 sessions for 104 weeks) or continue with an antidepressant of their choice. No significant differences in mean HRSD or BDI scores were found between the groups. The low retention rate (<35%), lack of statistical power and lack of operational definition of treatment resistance were limitations of the study. RCT 1-

The updated systematic review of Trivedi et al.[231] included a good quality RCT[238] evaluating cognitive therapy as a strategy for enhancing standard treatment in 469 patients with resistant depression belonging to 73 primary care centres. Participants were randomised to receive cognitive therapy + standard therapy or standard therapy alone (which included drug treatment) and followed up after 12 months. Patients in the intervention group (CBT) received 12 to 18 sessions of cognitive therapy for 6 months. Treatment-resistant depression in patients were defined as meeting the criteria for major depressive disorder according to ICD-10 and having a BDI scale score ≥ 14 after successful adherence to a drug treatment programme of at least 6 weeks. At 6 months and after an intention to treat analysis, the CBT group showed a reduction of 12.9 points on the BDI scale vs. 7.3 in the standard therapy control group. The response rates (50% reduction in BDI score from baseline) and remission rates (BDI <10) were 46% and 28% for the intervention group, respectively, and 22% and 15% for the control group, which were statistically significant differences. RCT 1+

Evidence summary

1+	Enhancement with cognitive therapy or a second antidepressant (bupropion or buspirone) for patients with an inadequate response to initial treatment with citalopram had no significant difference in either the percentage remission or the mean QIDS-SR scale scores[233].
1+	Patients with inadequate response to initial treatment with citalopram had either 16 sessions of CBT for 12 weeks or treatment with bupropion, sertraline or venlafaxine as a replacement. No significant differences in either the percentage remission or the mean QIDS-SR scale scores[233] were found.

1+	Patients with resistant depression and partial remission of depressive symptoms had no significant difference in their HRSD scores when compared with patients who received a combination of cognitive therapy plus standard treatment or the latter alone[234].
1-	A small sample size RCT compared patients with resistant depression receiving dialectical behaviour therapy (DBT) with those on the waiting list for it; better HRSD scale scores were observed in the DBT group. Both groups were able to continue with drug therapy, while the DBT group was able to continue with individual psychotherapy, as long as it was not cognitive therapy[235].
1+	Enhancement with 12 sessions of cognitive therapy in patients with resistant depression achieved worse HRSD scale scores than enhancement with lithium, although no significant differences were found in the BDI scale scores[236].
1-	No significant differences in the mean HRSD or BDI scores were found in patients with resistant depression when comparing enhancement with cognitive therapy and continuing with an antidepressant[237].
1+	The combination of cognitive therapy plus standard treatment (which included drug treatment) showed a reduction of 12.9 points on the BDI scale compared with 7.3 in the standard therapy control group for primary care patients with resistant depression. The response and remission rates were respectively 46% and 28% for the intervention group, and 22% and 15% for the control group, which were statistically significant differences238.

Recommendations

B	A combined therapy of cognitive behavioural therapy and antidepressant pharmacotherapy is recommended for patients with resistant depression.

8.2 Pharmacological strategies in resistant depression

Key question:

- What pharmacological strategies are most effective in patients with treatment-resistant depression?

It has been estimated that approximately 20 to 30% of patients with depression do not respond to initial drug treatment, despite receiving the appropriate dose and duration13. When an inadequate dose is given or treatment time is too short, the lack of response is called pseudoresistance[230].

In cases of no or partial response to drug treatment, the factors outlined in Table 17 should always be checked for.

Table 17. Main factors to assess for no or poor response to drug treatment in depression

– Review of diagnosis.
– Compliance with treatment dosage and time.
– Awareness of illness and motivation to change.
– Existence of possible comorbidity.

Source: Prepared by the authors

The pharmacological strategies considered in this section are:

- Increasing dose
- Switching to another antidepressant
- Combination of antidepressants
- Enhancement of antidepressant treatment with another drug:
    - Antipsychotics
    - Lithium
    - Anticonvulsants
    - Triiodothyronine
    - Pindolol
    - Zinc
    - Benzodiazepines

8.2.1 Increasing dose

A systematic review[239] of 11 studies that examined increased antidepressant dose in patients refractory to medical therapy, among other strategies, obtained the following results: SR 1+

- No difference in efficacy in patients with a partial response to 20 mg/day of fluoxetine for 8 weeks was found if the dose was increased to 40-60 mg/day or combined with desipramine or enhanced with lithium.
- Patients unresponsive to an initial 3-week treatment with SSRIs (fluoxetine, paroxetine, sertraline) achieved no significant improvement in the results when comparing the increase with the maintenance dose; in fact, an increase in the drop-out rate was found due to adverse effects.
- Patients not responding after 6 weeks of treatment with 100 mg/day of sertraline had a lower response rate when the dose was increased to 200mg/day, compared with maintaining the initial dose or enhancing with 30mg of mianserin.

The NICE guideline[13] selected 9 studies comparing different doses of drugs after a lack of response to the initial dose, of which only 1 was not included in the previous review, and basically assessed the tolerability of duloxetine[240]. The authors considered there was little evidence that increasing the dose improved outcomes compared to maintaining the same dose. However, because there are few studies and since it is known that there are individual differences in the hepatic metabolism of antidepressants, it seems reasonable to consider this possibility, while remaining within the therapeutic range; particularly when the response has been partial and the side effects are not significant. The British Association of Psychopharmacology guideline also recommended increasing the dose in these circumstances, especially when the antidepressant has a possible dose-response relationship[172]. RCT 1+

Subsequently, a RCT[241] was found that evaluated the tolerability and efficacy of 2 treatment modalities in 474 patients with severe depression and a lack of response (< 50% change in MADRS after 2 weeks of treatment with 10 mg/day escitalopram). The patients were randomised to receive 20 mg/day of escitalopram or 60 mg/day of duloxetine. At 8 weeks, the escitalopram treatment had significantly improved MADRS scale scores, with no differences between the groups in rates of abandonment. Moreover, a higher percentage of patients achieved remission with escitalopram (54%) than duloxetine (42%) with no differences in adverse effects. The percentage of patients with at least 1 adverse effect was 62% with the 10mg escitalopram dose, compared to 76% with the 20mg dose and 78% with duloxetine. Limitations of the study include a lack of a placebo group, no comparison with a 10mg escitalopram dose group to differentiate from improvement produced by either longer treatment duration, increasing the dose or changing antidepressant; there were also possible conflicts of interest due to the fact that a pharmaceutical company funded and ran the study.

RCT 1-

8.2.2 Switching to another antidepressant

The NICE guideline[13] included 3 RCTs comparing continuing with nortriptyline, fluoxetine or venlafaxine with changing to fluoxetine, mianserin or fluoxetine, respectively. There was no evidence to suggest any were more efficacious (as measured by the change in self-administered scale scores for response rate and remission) or tolerable (as measured by side effects).

RCT 1+

The NICE guideline[13] also included 4 RCTs and 1 open study in which changing antidepressants was investigated: switching to venlafaxine vs. switching to an SSRI (citalopram or paroxetine), and switching to olanzapine and fluoxetine vs fluoxetine[242/246]. These studies suggest some benefit for venlafaxine and escitalopram which, although it cannot be considered clinically important, could be relevant for patients who do not respond to the first or second antidepressant.

RCT 1+

Open label study 2

Subsequent to these studies, 4 new articles were included.

Fang et al.[247] conducted a RCT to evaluate the efficacy and tolerability of changing or continuing with antidepressant treatment in a population of 150 patients with major depressive disorder and at least 2 previous consecutive failures with antidepressants. Patients who were previously treated with paroxetine, were randomised to continue with paroxetine or change to venlafaxine XR or mirtazapine for 8 weeks. The remission rate (≤ 7 on the HRDS scale) was 42% for venlafaxine, 36% for mirtazapine and 47% for paroxetine, without significant differences. There were also no significant differences in response rates.

RCT 1+

Rosso et al.[248] conducted another RCT in 46 patients with depressive disorder resistant to 2 SSRI treatments of therapeutic doses for at least 4 weeks. Patients were randomised to duloxetine (120 mg/day) or bupropion delayed release (300 mg/day) for 6 weeks. A total of 60-70% of patients responded to treatment and 30-40% achieved remission at 6 weeks, with no significant differences between the groups. The limitations of this study include the method of randomisation and small sample size.

RCT 1+

In another study[249], 566 patients with less than 30% reduction in the HRSD scale after 4 weeks of treatment with escitalopram (10 mg/day) were randomised into the following treatment groups: arm A - switch to duloxetine (60-120 mg/day for 12 weeks); arm B - 4 more weeks with escitalopram (10-20 mg/day), then non-responders (reduction in HRSD ≤ 50%) were switched to duloxetine (60-120 mg/day for 8 weeks) while responders continued with escitalopram. The response rates were similar between the two arms, but those in remission were significantly higher in the duloxetine group. A limitation of the study was that only one third of the patients improved clinically after 4 weeks of treatment with 10 mg/day escitalopram; suggesting that, although this is the recommended dose, it might be low for patients with moderate to severe major depression. This low percentage of patients showing improvement could also explain the relatively high percentage of respondents after changing to an optimised dose of escitalopram.

RCT 1+

Finally, an open study design[250] randomised 189 patients unresponsive to at least one 4-week antidepressant treatment (other than citalopram or desipramine). The patients received either citalopram or desipramine for the first 4 weeks, and non-responders were treated for 4 weeks with the same antidepressant or switched to an alternative. In the first 4 weeks, the authors found no difference between citalopram and desipramine in HRSD, MADRS and CGI scale scores. In the second 4 weeks, the remission rate was higher for those who did not change their antidepressant (P = 0.04), although patients who switched drug received better HRSD and MADRS scale scores (P ≤ 0.02).

Open label study 2+

8.2.3 Combining an antidepressant with another antidepressant

The NICE guideline[13] included 7 studies comparing results from the administration of 2 antidepressants versus monotherapy at a standard or high dose, with no new studies added since the 2004 guideline. The combinations were:

a) SSRI + mianserin vs SSRIs[251-253].

b) Fluoxetine + desipramine vs high doses of fluoxetine[254,255].

c) Antidepressant +mirtazapine vs antidepressant[256].

d) Sertraline + mianserin vs high doses of sertraline + placebo[252].

From these studies, the NICE guideline[13] considered a combination of 2 antidepressants tended to produce better results in response, remission and average final scores compared to a single antidepressant at standard doses; although there was insufficient evidence at high doses. Sometimes the combination of drugs is associated with more side effects.

RCT 1+

Following these studies, 1 new article was selected.

Seguí et al. [257] conducted a multicentre, open-label, non-randomised 12-week study of 79 patients diagnosed with major depression resistant to previous treatment with duloxetine monotherapy at the recommended maximum dose (reduction < 50% in depressive symptoms, as measured by the Hamilton scale, after 8 weeks of treatment). Patients received a combination of duloxetine (initial dose) and reboxetine (2-8 mg/day). At 12 weeks, a significant reduction in the HRSD scale score of 65.5% was observed, with the response rate 76% and remission rate 69%; the CGI scale reduction was also significant (68.5%). The most common side effects were dry mouth, sweating, constipation and difficulty urinating.

Case series, 3

8.2.4 Augmenting an antidepressant with antipsychotics

NICE[13] included 8 RCTs that addressed the enhancement of antidepressants with antipsychotics (aripiprazole, olanzapine, risperidone and quetiapine) in patients with resistant depression. Our update includes 8 new RCTs and a subsequent open-label study.

Augmenting with aripiprazole

The NICE guideline included 2 RCTs[258,259] evaluating enhancement of a treatment with a SSRI or venlafaxine with aripiprazole and found better results, although not significant, for depression scale scores and response and remission rates (36% and 25%, respectively, in the first group and 27% and 15%, respectively, in the second). No significant differences in the rate of early discontinuation of therapy due to side effects were observed.

RCT 1+

A RCT conducted by Fava et al.[260] evaluated the efficacy of low doses of aripiprazole as an enhancer in patients with major depression and inadequate response to up to 3 drug trials with SSRIs or SNRIs at suitable doses for at least 8 weeks. The study was divided into 2 phases of 30 days each: 221 patients were randomised to drug-drug (DD), placebo-placebo (PP) and placebo-drug (PD) groups. The DD group received 2 mg/day of aripiprazole + an antidepressant (AD) during the first 30 days, which increased to 5 mg aripiprazole/day for the remaining 30 days. The PP group received placebo and a AD for 60 days and the PD group received placebo + AD for the first 30 days and placebo + AD + 2g/day aripiprazole for the remaining 30 days. The most common concomitant ADs were duloxetine, escitalopram, fluoxetine and sertraline. The response rate (measured by the MADRS scale) for aripiprazole (2 mg/day) was 18.5% in phase 1 and 18% in phase 2; for placebo, it was 17.4% in phase 1 and 7.9% in phase 2. The difference in response rate between aripiprazole and placebo jointly in the 2 phases was 5.6% and the difference in remission rate was 2.3%; both of these differences were statistically insignificant. The most common side effects with aripiprazole were constipation, weight gain and dry mouth.

RCT 1+

Fabrazzo et al.[261] studied 35 adults with recurrent major depression and a history of not responding to an adequate dose of SSRI for 6 weeks. The patients did not adequately respond to a subsequent treatment with clomipramine for 6 weeks, with 5mg of aripiprazole being used as an enhancer of clomipramine. The results were measured at 4, 8 and 24 weeks after starting this treatment. The HRDS scale scores decreased significantly every week: the response rates at week 4, 8 and 24 were, respectively, 11%, 57% and 91%; while the remission rate was 0%, 0% and 34%, respectively, for the same timepoints. Case series, 3

Augmenting with olanzapine

Included in the NICE guideline were 2 RCTs[262,263] evaluating enhancement with olanzapine of pre-treatment with fluoxetine. The depression scale results were better for the enhancement group than for the placebo group, although not significantly; as were the response and remission rates (41% and 27%, respectively, in the first group and 28% and 16%, respectively, in the second). The percentage of early discontinuation of treatment due to adverse events was 13.5% in the olanzapine group and 2.4% in the placebo group. RCT 1+

Trivedi et al.[264] conducted an assessment of all studies combining olanzapine and fluoxetine (COF) in treatment-resistant depression. Included were 5 trials (published in 4 articles); 3 compared COF with fluoxetine and olanzapine[263,265]; 1 compared COF with fluoxetine, olanzapine, and nortriptyline[262]; and 1 compared COF with fluoxetine, olanzapine and venlafaxine[242.] However, only those patients randomised to the COF groups, fluoxetine and olanzapine groups were included in the analysis. The study design was very similar and all patients had to have documented proof of not responding to at least 2 prior antidepressant treatments. In all trials, there was a first open phase lasting 6-8 weeks designed to verify resistance. Those patients who showed no improvement after this first phase were randomly assigned to the COF group (n = 462), the fluoxetine group (n = 342) or olanzapine (n = 342) for 8-12 weeks of double-blind treatment. The average olanzapine and fluoxetine dose in these studies ranged between 9-13 mg/day and 37-52 mg/day, respectively. At 8 weeks, patients in the COF group showed a greater and significant improvement in MADRS scores than the fluoxetine or olanzapine groups; with remission rates of 26%, 17% and 14% for the COF, fluoxetine and olanzapine groups, respectively. The adverse effects of the combination of olanzapine and fluoxetine were consistent with those of its components, i.e. weight gain, increased appetite, dry mouth, drowsiness, fatigue, headache and oedema appearing in ≥10%. RCT 1+

Augmenting with risperidone

Included in the NICE guideline were 3 RCTs[266-268] evaluating enhancement with risperidone of prior treatment with various antidepressants. The differences in the depression scale results were not significant between the enhancement group and the control (35% and 23% in the first group, and 3% and 22% in the second group, respectively). No significant differences were observed in the rate of early discontinuation of treatment due to side effects. RCT 1+

Fang et al.[269] conducted a RCT evaluating enhancement in patients with major depression and prior failure of 2 or more different antidepressant treatments. The 225 patients were randomised to receive paroxetine enhanced with risperidone (RI), valproic acid (VA), buspirone (BU), trazodone (TR) or triiodothyronine (T3). The overall response rate was 56.9%, the remission rate was 37.3%; and 86% of patients completed the 8-week treatment programme. For each drug, the respective percentages of response and remission were: RI: 46.7%, 26.7%; AV: 61.5%, 48.7%; BU: 56.5%, 32.6%; TR: 61.7%, 42.6%; and T3: 58.3%, 37.5%. The differences between the groups were not significant. The most common side effects were dry mouth, loss of appetite, weight gain, nausea and vomiting, tremor and fatigue. The limitations of the test were the lack of a comparative placebo arm, the modest sample size to see differences between groups, the fixed treatment doses and low external validity, as it was performed exclusively on a Chinese population. RCT 1+

Augmenting with quetiapine

The NICE guideline included a single RCT[270] that evaluated enhancement with quetiapine of prior treatment with a SSRI or venlafaxine. The rates of response and remission in the enhancement group were respectively 48% and 28%, while the control group was 31% and 17%, with no statistical significance between them. The first group also obtained better scores on depression scales and in no case were significant differences in the results obtained. The percentage of early discontinuation of treatment due to adverse events was 27.6% for the quetiapine group compared to 6.9% in the control group. RCT 1+

Bauer et al.[271] conducted a grouped study of the above 2 trials[272,273], in which patients received quetiapine XR at doses of 150 or 300 mg/day, or placebo, to enhance the antidepressant treatment. Both doses of quetiapine significantly reduced the MADRS scale score compared to placebo in both the first and the sixth week. The response rates (≥ 50% reduction in the MADRS score) after completing treatment were 54%, 58% ($p<0.01$) and 46% for quetiapine 150mg, 300mg and placebo, respectively. The remission rates (total score ≤ 8 in the MADRS scale) was 36% ($p<0.01$), 37% ($p<0.001$) and 24%, respectively. Compared with placebo, quetiapine doses of 150 and 300 mg/day significantly improved HRSD, HAM-A, PSQI and CGI-S scale scores in the sixth week. The limitations of this study were the use of a fixed dose and the absence of an active comparator. RCT 1+

Another RCT[274] evaluated the efficacy and tolerability of quetiapine as adjunctive in 58 patients with major depressive disorder, comorbid anxiety and residual depressive symptoms who had previously received SSRI/venlafaxine at therapeutic doses for ≥ 6 weeks. Patients were randomised to receive quetiapine or placebo plus SSRI/venlafaxine; and 62% of patients receiving quetiapine completed the study compared to 55% of those receiving placebo. The response and remission rates were higher for quetiapine than placebo, although not significant (response: 48% vs. 28%; remission: 31% vs. 17%). The adverse effects for quetiapine were similar to those previously observed. RCT 1+

An open label study275 compared quetiapine with lithium as an adjunct to antidepressant treatment in patients with major depression who had not achieved a response rate after 4 weeks of treatment with the maximum recommended dose. The 20 patients included were randomised to receive lithium or quetiapine, while continuing with prior antidepressant treatment and other concurrent medications (mainly anxiolytics and hypnotics). The depressive symptoms, as measured by the HRSD scale, were significantly reduced in both groups compared to baseline, although more so for quetiapine.

Open-label study 2+

Enhancement with different antipsychotics

Yoshimura et al.[276] included 45 patients (19 of them with psychotic symptoms) diagnosed with major depression (n = 31) or bipolar disorder (n = 14). The patients were treated with antidepressants (sertraline, paroxetine, minalcipram or fluvoxamine, n = 35) or mood stabilisers (lithium or valproic acid, n = 10) for at least 4 weeks, without achieving a complete response (reduction < 50% in the HRDS scale). The aim of the study was to evaluate the effect of enhancement of prior treatment with atypical antipsychotics (risperidone, aripiprazole, olanzapine, perospirone and quetiapine). The Hamilton scale scores at 0, 1, 2, 3 and 4 weeks of adding the antipsychotic were 19, 17, 14, 12 and 10, respectively, and the response rate was 42%. There were no differences between patients with major depression or bipolar disorder.

Case series 3

8.2.5 Augmenting an antidepressant with lithium

The NICE guideline[13] did not add any new study to the guideline produced in 2004[277], in which 10 trials assessed the efficacy of lithium as an enhancer of antidepressant treatment (clomipramine, desipramine, imipramine, nortriptyline or citalopram). Compared with placebo, the results showed significant differences in response rate in favour of lithium, although not in the remission rate. Lithium enhancement was less well tolerated by patients, with 30% of early dropouts compared to 17% in the placebo group, although the number of results was insufficient to determine whether the increased number of dropouts was due to adverse effects.

SR 1

Following these studies, 2 new articles were included.

The first[278] was part of the STAR*D study, and had 142 adult patients with nonpsychotic major depressive disorder who had not achieved remission or tolerated initial treatment with citalopram and a subsequent change or enhancement. They were randomised to an enhancement group with lithium or triiodothyronine (T3) for 14 weeks. After treatment, the remission rate was 16% with lithium and 25% with T3, which was not statistically significant. Lithium was more frequently associated with side effects, and this was the reason for the higher drop-out in this group.

RCT 1+

The other study[279] was of 20 patients considered resistant to drug therapy after a multi-step algorithm (paroxetine, paroxetine and enhancement with lithium and venlafaxine) who received 150 mg/day of clomipramine for 1 month. The patients who did not respond received enhancement with lithium or lithium + T3. The treatment with clomipramine achieved remission (MADRS ≤ 8) in 5 patients: 3 were responders (MADRS ≥ 50% reduction) and 3 partial responders (MADRS reduction > 25%). Lithium enhancement in 10 patients led to a further remission, while enhancement with T3 in 6 patients did not lead to further remission.

Case series 3

8.2.6 Augmenting an antidepressant with anticonvulsants

The NICE guideline[13] considered the lack of controlled data and the high probability of adverse effects or clinically significant interactions meant that neither carbamazepine nor valproic acid could be recommended as a treatment for major depression with inadequate response to treatment.

SR of different study types 2+

The NICE guideline[13] included 3 RCTs and an open-label study of enhancement with lamotrigine.

A RCT[280] of 40 patients with major depression (30 unipolar and 10 bipolar) undergoing paroxetine treatment received enhancement with lamotrigine or placebo for 9 weeks, with no difference found in the Hamilton scale scores for lamotrigine and placebo.

RCT 1+

Another study[281] of 23 patients with depression (65% with major depression) who had failed at least 1 prior antidepressant treatment were randomised to receive fluoxetine with either placebo or lamotrigine. No significant differences in the HRSD or MADRS scales between the two groups at 6 weeks were observed.

RCT 1+

Santos et al. [282] randomised 34 patients with depression, who had not responded adequately to at least 2 different classes of antidepressants for at least 6 weeks, for lamotrigine or placebo, in addition to continuing their previous drug. The results showed no advantages of enhancement with lamotrigine in depression scale scores.

RCT 1+

Finally, Schindler and Anghelescu[283] randomised 34 patients diagnosed with major depression and an inadequate response to 2 previous drug treatments for lamotrigine or lithium in an open-label study. At 8 weeks, no differences in HRSD scale scores or the percentages of response or remission were found between the groups.

Open-label study 2+

Following these studies, 2 new articles were included.

A RCT[284] of 96 patients with non-psychotic major depression and inadequate response (HRSD ≥ 15) to paroxetine treatment for 8 weeks were randomised to receive placebo or lamotrigine to enhance the paroxetine. Analysis of the study was by intention to treat and 68% of the patients completed the course. The results obtained in the MADRS, HRSD and CGI scale scores 10 weeks after randomisation showed no significant difference between treatment groups, although the analysis suggested some secondary efficacy variables, particularly in those patients who completed the study and in whom the depression was more severe. RCT 1+

Mowla and Kardeh[285] conducted a double-blind, randomised controlled trial on 53 patients with major depression and no response to at least 1 trial of 8 weeks of an adequate SSRI dose (fluoxetine, sertraline, citalopram). Patients were randomised to receive either a flexible dose of topiramate (100-200 mg/day) or placebo, in addition to continuing the SSRI. There were 11 drop-outs: 6 in the topiramate group, mainly due to adverse effects, and 5 in the placebo group due to lack of efficacy. The topiramate group had a statistically significant improvement in Hamilton depression scale scores compared to the placebo group, with a decrease in score of 32% compared with 6% in the control group. The number of respondents in the topiramate group was 12 (60%) compared to 0 in placebo group, and topiramate group patients significantly improved mood, suicidality, insomnia, agitation and anxiety symptoms. Limitations of the study included the small sample size, short follow-up time, the administration of various SSRIs in the enhancement and a lack of established dosages. RCT 1+

8.2.7 Augmenting an antidepressant with triiodothyronine

The NICE guideline[13] did not add any new study to the guideline produced in 2004[277], in which only 1 study with triiodothyronine (T3) was selected as enhancement for desipramine or imipramine treatment[286]. The comparison with placebo found significant differences in the response rate but not in reducing depressive symptoms. Furthermore, because of side effects, T3 should be used with caution in patients with cardiovascular disease, and should be used with caution in association with tricyclic antidepressants. RCT 1+

The lithium enhancement section refers to 2 new articles[278,279] which also assess the efficacy of T3.

8.2.8 Augmenting an antidepressant with pindolol

The NICE guideline[13] did not add any new study to the guideline produced in 2004[277,] in which 6 comparative studies assessed the enhancement of an antidepressant with pindolol or placebo. The authors concluded that, although there is evidence that adding pindolol favours remission in depressive symptoms, the effect is not evident in the response rate or the scale scores. No effects were observed in the initial assessments for treatment-resistant patients and with no longer term evaluation data. Finally, there were insufficient data concerning the tolerability of adding pindolol to an antidepressant, as well as not knowing clearly the optimal dose or treatment duration required. RCT 1+

No new study was included in the update.

8.2.9 Augmenting an antidepressant with zinc

The NICE guideline[13] did not include any study in this section, and only 1 study is selected in this update

Siwek et al.[287] conducted a RCT with 52 adults with unipolar major depression without psychotic symptoms. Patients were classified as resistant or not to prior treatment and randomised to receive imipramine + placebo or imipramine + zinc for 12 weeks. No significant differences were found in CGI, BDI, HRSD and MADRS scale scores for either the enhancement treatment arm in non-resistant patients; however, for resistant patients, the zinc enhancement group obtained significant reductions in the scores, compared with placebo. RCT 1+

8.2.10 Augmenting an antidepressant with benzodiazepines

The role of benzodiazepines as an enhancer of antidepressant treatment was reviewed in the NICE guideline[13,] without including any new study since the 2004 guide[277,] in which 5 comparative studies enhancing an antidepressant (maprotiline, nortriptyline, fluoxetine, imipramine and amitriptiline) were evaluated with a benzodiazepine (flunitrazepam, lormetazepam, clonazepam, diazepam or chlordiazepoxide). The authors found no conclusive evidence of the existence of any effect of adding a benzodiazepine to antidepressant treatment in terms of tolerability or efficacy. RCT 1+

Evidence summary

Increasing dosage	
1+	In the absence of response, there is little evidence that increasing dosages is more effective than maintaining the dose; there are a limited number of studies comparing these strategies[13,172,239].
1+	Although there is no conclusive evidence, this strategy has been recommended due mainly to individual differences in the hepatic metabolism of antidepressants, within the established range at all times, and particularly when there has been a partial response and side effects are tolerated[13,172].
1-	Increasing the dose of escitalopram from 10mg to 20mg increased the percentage of patients with response or remission in one trial, although with a higher rate of side effects[241].
Switching to another antidepressant	
1+	No evidence was found in 3 studies of patients with depression unresponsive to initial pharmacological treatment with nortriptyline, fluoxetine or venlafaxine who changed to fluoxetine, mianserin and fluoxetine, respectively, for improvements in efficacy (change in self-administered scale scores, or response or remission rates) or tolerability (side effects)[13].
1+	There is some evidence of efficacy of venlafaxine and escitalopram from studies comparing change strategies and, although this difference may not be clinically relevant when considering the patients with depression in general, it could be important for patients with resistant depression[13].

1+	No significant changes in the response or remission rates were found in patients with major depressive disorder and at least 2 previous consecutive failures with antidepressants, for continuing with paroxetine or switching to venlafaxine XR or mirtazapine for 8 weeks[247].
1+	Patients with depression resistant to 2 SSRI treatments at therapeutic doses for at least 4 weeks found no significant difference between groups switching to duloxetine or bupropion, with response rates of 60-70% and remission rates 30-40% [248].
1+	The response rate was similar for patients, with little or no response after 4 weeks of treatment with 10 mg/day of escitalopram, who continued with 10-20 mg/day of escitalopram or who changed to duloxetine; although remission was significantly higher in the group that switched to duloxetine[249].
3	Patients who did not respond to at least 1 treatment with an antidepressant received citalopram or desipramine for 4 weeks; non-responders were then treated for 4 weeks with the same antidepressant or were changed to an alternative. No differences between citalopram and desipramine were observed in the HRSD, MADRS and CGI scale scores in the first 4 weeks; while remission rates were higher among those who continued with the same antidepressant in the second 4 weeks[250].
Combining an antidepressant with another antidepressant	
1+	There is some evidence that a combination of antidepressants (mainly with mirtazapine and mianserin) tends to reduce symptoms compared with continuing with the same antidepressant, although the participants receiving the combination had more side effects[13].
3	The combination of duloxetine at the initial dose and reboxetine, in patients with major depression resistant to previous treatment with duloxetine, reduced the HRSD scale score by 66%, with a response rate of 76% and remission rate of 69%[257].
Augmenting an antidepressant with an antipsychotic	
1+	Enhancement with aripiprazole, after prior treatment with a SSRI or venlafaxine in patients with resistant depression, did not obtain significantly better results, depression scale scores or response or remission rates; nor were there significant differences in the rate of early discontinuation of treatment due to side effects[258,259].
1+	Low doses of aripiprazole as an enhancer did not obtain significant differences with the control group for the rate of response or remission in patients with major depression and an inadequate response to 1 or more trials with SSRIs or SNRIs[260].
3	Aripiprazole as a tricyclic enhancer significantly decreased the HRDS score scale, with a response rate of 91% and remission rate of 34% at 24 weeks in patients with recurrent major depression and no history of response to a trial of SSRIs and later clomipramine[261].
1+	Enhancement of fluoxetine treatment with olanzapine did not obtain statistically significant differences from placebo in depression scale scores or rates of response or remission, although the results were somewhat better. However, the percentage of early discontinuation of treatment due to adverse effects was higher for the enhancement group[262,263].

1+	A systematic review of 5 studies[264] evaluating the combination of olanzapine and fluoxetine in patients with resistant depression was performed. The analysis was of those patients randomised to the COF, fluoxetine or olanzapine groups, although other drugs were included. After an initial open phase of 6-8 weeks to check resistance, patients without improvement were randomised to the COF (n = 462), fluoxetine (n = 342) or olanzapine (n = 342) group for 8-12 weeks. The average dose of olanzapine and fluoxetine ranged from between 9-13 mg/day and 37-52 mg/day, respectively. At 8 weeks, patients in the COF group showed greater MADRS score improvement than the fluoxetine or olanzapine groups, which was significant; the remission rates were 26%, 17% and 14% for the COF, fluoxetine and olanzapine groups, respectively. The adverse effects of the combination of olanzapine and fluoxetine were consistent with its components; i.e. ≥ 10% experienced weight gain, increased appetite, dry mouth, drowsiness, fatigue, headache or oedema.
1+	Enhancement with risperidone after prior treatment with various antidepressants was evaluated in 3 RCTs[266-268]. The enhanced group scored better on depression scales, with better rates of response and remission than the control group, although the results were not statistically significant. No significant differences were observed in the rate of early discontinuation of treatment due to side effects.
1+	Enhancement with risperidone obtained a response rate of 47% and 27% for remission, with no significant differences obtained by valproic acid, buspirone, trazodone and triiodothyronine, in patients with major depression and prior failure on 2 or more treatments with different antidepressants[269].
1+	A RCT of quetiapine enhancement of previous treatment with an SSRI or venlafaxine did not obtain significantly different results from the control group, although scores on the depression scales and rates of response and remission were better. The percentage of early discontinuation of treatment due to adverse events was 28% for the quetiapine group versus 7% in the control group[270].
1+	A pooled study of 2 previous trials in patients with resistant depression assessed enhancement of the treatment with 150 or 300 mg/day of quetiapine or placebo. After 5 weeks, both doses of quetiapine significantly reduced the score on the MADRS scale and had higher remission rates than placebo, while only the response rate after 300 mg/day quetiapine was significantly greater than placebo[271].
1+	Another RCT[274] evaluated the role of adjunctive quetiapine in patients with major depressive disorder, comorbid anxiety and residual depressive symptoms who had previously received SSRIs/venlafaxine at therapeutic doses for ≥ 6 weeks. Patients were randomised to receive quetiapine or placebo plus SSRIs/venlafaxine; with rates of response and remission statistically similar, although higher for quetiapine than placebo.
2+	An open label study[275] compared quetiapine with lithium as an adjunct to antidepressant treatment in patients with major depression who had not responded after 4 weeks of treatment with the maximum recommended dose. The HRSD scale score decreased significantly in both groups from baseline, although more so for quetiapine.
Augmenting an antidepressant with lithium	
1+	The NICE guideline[13] included 10 trials evaluating the efficacy of lithium as an enhancer of antidepressant treatment (clomipramine, desipramine, imipramine, nortriptyline or citalopram). Compared with placebo, the results showed significant differences in favour of lithium in response rate, but not in remission rate. The drop-out rate was higher in the lithium enhancement group.

1+	As part of the STAR*D study[278], lithium enhancement was evaluated in patients with major depressive disorder who had not achieved remission with citalopram and a subsequent change or enhancement. It obtained a remission rate of less than T3. Furthermore, it was more frequently associated with side effects and drop-out for this reason.
3	A study was performed with 20 drug treatment resistant patients receiving 150 mg/day clomipramine for 1 month. Those with no response received lithium enhancement with lithium or lithium + T3. Treatment with clomipramine alone was sufficient for response in 3 patients and remission in 5. Lithium enhancement in 10 patients led to a further remission, while enhancement with T3 in 6 patients failed to obtain further remission[279].
Augmenting an antidepressant with anticonvulsants	
1+	For the NICE guideline[13], the lack of controlled data and the high probability of adverse effects or clinically significant interactions mean that both carbamazepine and valproic acid could not be recommended as a treatment for major depression with inadequate response to treatment.
1+	Enhancement with lamotrigine had similar results to placebo for depression scale scores in patients with major depression resistant to treatment with paroxetine280, fluoxetine281 and 2 different classes of antidepressants[282].
2+	Enhancement with lamotrigine and lithium were compared in an open label design study[283] after 2 previous drug trials; no differences in HRSD scale scores or percentages of response or remission were found.
1+	No significant differences in MADRS, HRSD or CGI scale scores after enhancement with lamotrigine or placebo were observed for patients with major depression and inadequate response to previous treatment with paroxetine for 8 weeks[284].
1-	Patients with resistant depression in a study with a high risk of bias[285] were randomised to receive either a flexible dose of topiramate or placebo, in addition to continuing with prior SSRI (fluoxetine, sertraline, citalopram). The topiramate group had a statistically significant reduction in the Hamilton depression scale and a higher response rate than the placebo group.
Augmenting an antidepressant with triiodothyronine	
1+	The NICE guideline[13] included a single study in which T3 was used as enhancement for imipramine or desipramine treatment. The comparison with placebo found significant differences in response rate, but not in reducing depressive symptoms. Furthermore, triiodothyronine should be used with caution in patients with cardiovascular disease because of side effects and should be used with caution when associated with tricyclic antidepressants.
Augmenting an antidepressant with pindolol	
1+	The NICE guideline[13] included 6 comparative studies of enhancement of an antidepressant with pindolol or placebo and, although there is evidence that adding pindolol favours remission of depressive symptoms, the effect is not evident in the percentage response or the scale scores.

Augmenting an antidepressant with zinc	
1+	Treatment with imipramine + zinc for 12 weeks in patients with major depression and a history of resistance to drug therapy significantly reduced the CGI, BDI, HRSD and MADRS scores compared with those receiving imipramine + placebo[287].
Augmenting an antidepressantwith benzodiazepines	
1+	No conclusive evidence was found for any effect of adding a benzodiazepine to antidepressant treatment in terms of tolerability or efficacy[13].

Recommendations

√	The following is recommended for patients who do not improve with initial antidepressant treatment for depression: - Review of diagnosis. - Verify compliance with taking the appropriate dosage and treatment time. - Assess the existence of disease awareness, motivation to change and possible comorbidity
√	The following is recommended for patients with a partial response after the 3rd or 4th week: - Wait for clinical evolution until the 8th week. - Increase the drug dose to the maximum therapeutic dose.
B	If the patient does not respond by the 3rd or 4th week of treatment, any of the following strategies could be attempted: - Change of antidepressant to another in the same or a different family. - Combination of antidepressants. - Enhancement with lithium or antipsychotics.
C	When the strategy is changing the antidepressant, a different SSRI or another second-generation antidepressant should initially be evaluated. If there is no response, an antidepressant with greater side effects, such as a tricyclic or MAOI, could be assessed
C	The combination of SSRI and mianserin or mirtazapine may be a recommendable option, bearing in mind the possibility of adverse effects.
C	Enhancement with lithium or antipsychotics, such as olanzapine, quetiapine, aripiprazole or risperidone may also be a strategy to consider, bearing in mind the possibility of greater adverse effects.
D$^{\text{GPC}}$	When enhancement or a drug combination is used: - Be aware that these strategies usually increase adverse effects. - Select those drugs for which there is information on safety in combined use. - Document the rationale for the strategy. - Monitor carefully for adverse effects.
√	There are insufficient data to recommend enhancement with carbamazepine, lamotrigine, topiramate, valproate, pindolol, thyroid hormones, zinc or benzodiazepines.

8.3 Electroconvulsive therapy

Key question

- What is the safety and efficacy of electroconvulsive therapy as a treatment for depression?

Electroconvulsive therapy (ECT) induces a generalised seizure by electrical stimulation of the central nervous system. Studies have shown that ECT is effective in severe depressive episodes and resistant depression and could be considered a first-line treatment in acute suicide risk situations or patients with severe mental impairment[51,277,288]. However, although ECT has been in use in clinical practice for more than 70 years, it remains controversial. Thus, it is seen by many professionals as a safe and effective way to treat severe depression[67,] while others consider it an outdated and potentially harmful technique, as do some groups of patients[289].

Unilateral implementation is usually performed in the non-dominant hemisphere to reduce adverse cognitive effects. When the location of the electrodes is bilateral, it is done in the bitemporal or temporofrontal region, although some studies have used the bifrontal location to reduce adverse effects. Stimulus parameters can vary widely (pulse width of 0.3-1 msec, frequency 20-120 Hz, stimulus duration 0.5-8 secs) and they are adjusted individually for each patient. The number of sessions is usually 6-12, although there is no maximum number, and are usually within a scheme of 2-3 sessions.

ECT has no absolute contraindications, although there are relative risk situations: presence of space-occupying lesions (tumours or haemorrhages) or any other situation in which the intracranial pressure is increased, recent serious cardiovascular disease, treatment with MAOIs or lithium and the risks from general anaesthesia itself. Side effects can be immediate (confusion, amnesia and headaches) or long-term (mainly cognitive impairment) and depend on the preconditions of patients, their personal susceptibility, the technique used (bilateral or unilateral), the number of sessions employed and administration frequency[288].

A search of clinical practice guidelines (CPG), systematic reviews, meta-analyses and primary studies was performed using a selection of items specifically for this technique to address the safety and efficacy of electroconvulsive therapy in the treatment of major depression. As in other sections, the CPG used as a reference was that of the National Institute for Health & Clinical Excellence (NICE)[13], as well as its update; this included the systematic review and meta-analysis of Dunne et al.[290], in which bifrontal ECT was compared with bilateral and unilateral ECT in the treatment of depression. No primary studies subsequent to these reviews were selected.

8.3.1 Safety and efficacy of electroconvulsive therapy in the treatment of depression

The 2009 NICE treatment and management of depression in adults CPG[13] found no new studies from the previous version[277], which compared real and sham ECT, antidepressants and combined treatments in the acute phase. In addition, the new contributions on their use during the continuation phase after acute treatment are very limited. SR 1+

The conclusions about the safety and effectiveness of electroconvulsive therapy are the same as those contained in the 2004 CPG[277] and are summarised below:

- It is an effective treatment for severe major depression in adults, and is more effective than the sham version.
- Bilateral application is more effective than unilateral.
- There is a risk of developing short-term cognitive side effects.
- It is more effective than short-term treatment with some antidepressants.
- The combination of ECT with pharmacotherapy has shown no greater short-term effect than ECT alone.
- Preliminary studies show that ECT is more effective than repetitive transcranial magnetic stimulation.
- In patients who responded to ECT, the continuation treatment with tricyclic antidepressants and/or lithium reduces relapse rate compared to placebo

The NICE guideline on antenatal and postnatal mental health recommended ECT for pregnant patients with severe depression and when the physical health of the mother or foetus is at risk[291]. SR 1+

8.3.1.1 Studies comparing bilateral electroconvulsive therapy with unilateral

The NICE CPG[13] updated the Geddes et al. systematic review and meta-analysis[292] with 8 new randomised clinical trials (n = 472). The result confirmed a small positive effect for bilateral ECT (bifrontal or bitemporal) versus unilateral, with a standardised mean difference size effect of -0.23 (31 studies; 1,693 participants). The new data did not change the conclusion that bilateral ECT was more effective than unilateral, although the effect size is small. A dose sub-analysis suggested that unilateral ECT at high doses (150% above the seizure threshold) could be at least as effective as bilateral ECT at the standard dose, although the data were insufficient for quantitative analysis. SR 1+

Dunne et al. 2012[290] performed a meta-analysis of 6 RCTs (n = 201) comparing bifrontal with unilateral right ECT (n = 199). The results showed similar efficacy between the two techniques (standardised mean difference -0.12). SR 1+

8.3.1.2 Cognitive side effects

The NICE CPG[13] updated the Geddes et al.[292] systematic review with new randomised clinical trials comparing different doses of bitemporal ECT with unilateral ECT (6 studies); bifrontal and unilateral ECT (4 studies); and bifrontal and bitemporal ECT (1 study). The conclusions were that bilateral ECT is more effective than unilateral, but may cause greater cognitive impairment. It was also observed that raising the stimulation above the seizure threshold increases the effectiveness of unilateral ECT, albeit at the expense of causing greater cognitive impairment; and that the unilateral positioning of the electrodes in the dominant hemisphere produces greater damage than when placed in the non-dominant. Ultimately, reducing the risk of cognitive impairment entails a decrease in effectiveness, unless more recent studies provide sufficient evidence on how to provide a better effectiveness/cognitive side effects ratio, by manipulating the dose and electrode placement. High-dose ECT with ultra short pulses (0.3 msec) was found not to cause cognitive impairment in 2 studies and, in another, the deterioration was significantly lower than with the standard brief pulse (1.5 msec). SR 1+

The Dunne et al. 2012[290] meta-analysis of 4 RCTs compared bifrontal ECT with bitemporal and found a smaller decrease in the Mini-Mental State Examination (MMSE) with the bifrontal technique, resulting in a difference of 1.38 points on the MMSE. Changes in MMSE were reported in 5 RCTs comparing bifrontal ECT with unilateral right ECT; no significant difference was observed between the two techniques. SR 1+

8.3.1.3 Relapse Prevention

The NICE guideline[13] assessed which was the most effective maintenance therapy after achieving response to electroconvulsive therapy. Two RCTs in which the maintenance therapy was ECT associated with nortriptyline versus continuation with nortriptyline[293] or ECT only versus nortriptyline + lithium[294]. Very little difference was observed between ECT with an antidepressant and maintaining the antidepressant alone, or between ECT administered alone and a combination of nortriptyline and lithium at 6 months. However, at 12 months, patients who had received ECT plus nortriptyline experienced fewer relapses than those who continued treatment with nortriptyline alone. Another 2 RCTs were included in which the maintenance strategy was drug treatment only: fluoxetine + placebo vs fluoxetine + melatonin[295], nortriptyline + lithium vs placebo, nortriptyline vs placebo, and nortriptyline + lithium vs nortriptyline[296]; only nortriptyline plus lithium was effective (compared to placebo) in preventing relapses. Although only 1 study compared each strategy and the sample sizes were small, it appears that combined treatment with nortriptyline and lithium could be effective in reducing the likelihood of relapse following successful treatment with ECT. A final RCT randomised patients who had managed a response with ECT to receive paroxetine or placebo (in those with cardiovascular disease) or paroxetine or imipramine in those without it; a benefit for paroxetine vs placebo and vs imipramine was found[297]. SR 1+

Schaik et al.[298] conducted a systematic review to evaluate the safety and efficacy of maintenance ECT in relapse prevention. It included all RCTs and cohort studies, both prospective and retrospective, in which at least 50% of patients had unipolar major depression, with a sample size greater than 5 and a mean age for the participants of 55 or more. Of the 3 RCTs included, 2 were the same as those included in the NICE guideline[293,294]. The third was a RCT[299] with a similar design to that of Navarro et al.[293.] After 2 years, a relapse or recurrence rate of 54% was found in the nortriptyline group and 17% in the ECT + nortriptyline (p = 0.0043). The 5 prospective studies are difficult to compare, as the patient selection methods, depression measurements, treatment durations, drug treatments and ECT procedures were all different. However, one could cautiously conclude that maintenance ECT was effective in older, drug-resistant patients or those with a long disease duration[298].The review also included 14 retrospective studies with methodological limitations, including 3 matched groups and the others without. All studies showed improvement after maintenance ECT in both clinical outcomes (relapse) and hospitalisation[298]. SR 1+, 2+

Evidence summary

1+	ECT is an effective treatment for adults with severe major depression. The electrical stimulus parameters influence the effectiveness, with the bilateral application being slightly more effective than the unilateral. ECT is a safe technique and the side effects on the memory are usually transient[13].
1+	An updated review of Geddes et al.[292] with 8 randomised clinical trials showed a small favourable effect for bilateral ECT (bifrontal or bitemporal) versus unilateral[13]. A meta-analysis of 6 RCTs comparing bifrontal ECT with right unilateral ECT showed similar efficacy for the 2 techniques[290].
1-	Bilateral ECT may cause greater cognitive impairment than unilateral. It has also been observed that raising the stimulation above the seizure threshold increases the effectiveness of unilateral ECT, albeit at the expense of greater cognitive impairment; also, the unilateral positioning of the electrodes in the dominant hemisphere produces greater damage than when placed in the non-dominant. Ultimately, reducing the risk of cognitive impairment entails a decrease in efficacy[13].
1+	It was observed in 2 studies that ECT at high doses with ultra short pulses (0.3 msec) did not cause cognitive impairment; and, in another, that this impairment was significantly lower than with standard short pulse (1.5 msec)[13].
1+	A smaller decrease in the Mini-Mental State Examination (MMSE) was found with bifrontal ECT when compared with bitemporal ECT in 4 RCTs. No statistically significant differences between bifrontal ECT and unilateral right ECT were observed in 5 comparative RCTs[290].

1+	In preventing relapse after ECT treatment, there was very little difference between adding ECT to an antidepressant and maintaining the antidepressant alone, and between administering ECT alone and a combination of nortriptyline and lithium at 6 months. However, at 12 months, patients who had received ECT plus nortriptyline experienced fewer relapses than those who continued treatment with nortriptyline alone[293,294]. In another 2 RCTs, in which the maintenance strategy was pharmacological only (fluoxetine + placebo vs fluoxetine + melatonin[295;] nortriptyline + lithium vs placebo; nortriptyline vs placebo; and nortriptyline + lithium vs nortriptyline[296)], it was observed that only nortriptyline plus lithium was effective in preventing relapses, compared with placebo. A final RCT randomised patients with a previous response to ECT to receive either paroxetine or placebo (in those with cardiovascular disease) and paroxetine or imipramine in those without it; paroxetine was found to be beneficial vs placebo and vs imipramine[297].
1+	A systematic review to evaluate the efficacy and safety of maintenance ECT in relapse prevention included 3 RCTs and 19 prospective and retrospective studies. Of the 3 RCTs, 2 showed a similar efficacy for continuing with ECT and with drug treatment, while the third[299] had a relapse or recurrence percentage much higher in the nortriptyline group compared with ECT + nortriptyline.
2+	The remaining studies showed improvements after maintenance ECT in both clinical outcomes (relapse) and hospitalisation[298].

Recommendations

A	Electroconvulsive therapy should be considered a therapeutic option in patients with severe depression; mainly if there is a need for a rapid response due to high suicidal intent, severe physical damage or when other treatments have failed.
√	ECT should always be given by experienced professionals, following a physical and psychiatric assessment and in a hospital setting; and informed consent is essential.
Q	The decision to use ECT should be made jointly with the patient and/or family, by taking into account factors such as diagnosis, type and severity of symptoms, medical history, risk/benefit ratio, alternative therapies and patient preference.
Q	Should ECT be required, it is recommended to place special emphasis on providing all the necessary information, focusing on the purpose of the procedure, the side effects and a treatment plan.

8.4 Vagus nerve stimulation as adjunctive treatment for resistant depression

Key question

- What is the safety and efficacy of vagus nerve stimulation as adjunctive treatment for resistant depression?

Vagus nerve stimulation (VNS) is an invasive subcutaneous procedure, consisting of a programmable generator inserted in the chest wall, similar to a cardiac pacemaker, which sends signals to the brain through the left vagus nerve. The procedure takes about 30-60 minutes under local or

general anaesthetic, and involves connecting the generator to a helical bipolar electrode placed around the vagus nerve at the fifth or sixth cervical vertebra[300,301]. The patient has a magnet with 3 possible settings: to provide a stimulus on demand, suspend the stimulation temporarily or make a daily check on the generator operation.

The goal of VNS in major depression is to improve the regulation of mood and reduce depression by impulses to the brain via the vagus nerve. Its history dates back to 1883, when Corning combined carotid compression with transcutaneous electrical stimulation of the vagus nerve to treat seizures. In 1938, Bailey and Bremen reported that stimulation of the central portion of the vagus nerve increased the electrical potentials in the orbital surface of the frontal lobe and, in 1951, Dell and Olson performed VNS in conscious cats. In 1985, Zabara postulated that cortical desynchronisation induced by vagal stimulation may have an antiepileptic effect and, in 1988, Penry implanted a device for VNS in humans. Subsequently, multicentre studies in the United States and Europe have confirmed the efficacy of vagal stimulation in patients with refractory epilepsy, and it was approved by the *Food and Drug Administration* (FDA) in 1997 as adjunctive therapy for reducing the frequency of seizures in refractory epilepsy treatment in adults and adolescents[302].

Clinical studies in patients with epilepsy found that the technique of vagus nerve stimulation may improve their mood[303]. This finding, together with the fact that the vagus nerve provides access to brain structures, led to studies to demonstrate its effectiveness in the treatment of depression[304-307]. In 2005, the FDA approved its use in patients over 18 years for the treatment of refractory major depressive disorder, defined as that for which there is no satisfactory response to 2 or more adequate antidepressant treatments.

8.4.1 Safety and efficacy of vagus nerve stimulation

Discussed below are 34 studies with a total of 2,170 patients from Daban et al. systematic reviews (18 studies)[308], 24 studies in the NICE guideline (18 of which correspond to the previous systematic review)[69] and 14 studies from Martin et al. (10 of which were not included in the previous reviews)[309].

Daban et al. systematic review (2008)[308]

In 2008, Daban et al.[308] published a systematic review that included 1,251 patients (with uni- and bipolar depression) from 18 studies. The only RCT[306] had no significant differences in HRSD scale scores between the group that received VNS and the sham group. However, there was a significant difference in favour of VNS when patients used the IDS scale for evaluation. In the rest of the studies, which were all observational in nature, the short-term response and remission rates observed were 30.5%, 15.3%[307], 40%, 17%[310], 57% and 29%[311], respectively. Other authors reported response rates of 40%[312] and 9%[313] Significant improvements were also observed in the HRSD score311 and the HRSD and IDS[313] scores compared to baseline. At 12 months, the response and remission rates observed were 46%, 29%[305], 58% and 36%[314], respectively.In another study, a response rate of 27% was found in the group receiving VNS and 13% in the group receiving standard therapy[315]. Significant improvements were also seen in the HRSD score from baseline[316,317]. One study[307] noted serious or clinically significant adverse effects in 17%,[10/59] patients: 2 patients had worse depression, and 1 had an AMI. Mania or hypomania occurred in 2% [2/112] of patients who received VNS. In the 6 short-term studies, 2 patients discontinued due to adverse events and 1 committed suicide. Other symptoms often reported by patients were hoarseness, headache, sore throat and neck pain. In general, the side effects in the studies were similar, mild in nature and limited in time.

SR of different studies, 1+, 3

National Institute for Clinical Excellence Systematic review (2009)[318]

The *National Institute for Clinical Excellence* (NICE)[318] issued a new systematic review in 2009 that included 24 studies: 18 corresponded to the Daban et al. systematic review[308] 2 were randomised clinical trials[319,320], a non-randomised controlled study[321] and 3 case series[322-324].

An RCT of 9 patients[319] found that the severity of depressive symptoms (measured with the HRSD scale) was associated with significant signal increases in the right temporal lobe, right insula and left middle frontal gyrus. Another RCT of [222] patients[320] found a response rate at 2 years of 33% in patients with unipolar depression and 38% in patients with bipolar disorder.

RCT 1+

A case series of 205 patients[323] found that 77% [23/30] of those who responded early maintained their response to VNS treatment at 24 months follow-up.

Case series 3

A case series[324] of 74 patients showed significant improvement in the HRSD scale score compared with baseline at 12 months follow-up, with 55% of patients responding at that time. Another case series[322] of 9 patients found no responsive patients after 1 week follow-up; however, the percentage of those responding was 56% and those in remission 44% at 12 months or more.

Case series 3

Finally, a non-randomised controlled study[321] of 18 patients found a significant decrease in the number of psychiatric consultations in the group receiving VNS compared with the drug therapy and psychotherapy group at 12 month follow-up.

Quasi-experimental study, 2+

The authors point out what was said in the Daban et al. SR regarding the safety of the technique. In addition, a case series[324] of 74 patients observed a suicide rate of 2% in 61 patients at 6 months follow up. At 3 months, 1% had had a manic episode, 1% had worse depression, 10% had dyspnoea and 20% experienced 'pain'. The most common adverse events were a cough and voice alteration (26% and 63% of patients, respectively, at 3 months). Case series 3

A case series[322] of 9 patients showed no serious adverse effects, although 100% had hoarseness which decreased over time. Case series 3

Martin et al. Systematic review (2012)[309]

The authors conducted a systematic review and meta-analysis to determine the efficacy and safety of VNS. They included 14 studies of which 8 were performed in [306] patients with depression[306,307,310,313,321,325-327] and 6 in patients with epilepsy (in which the depressive symptomatology was measured before and after the intervention)[303,304,328-331]. Previous systematic reviews had included 4 of the studies: 3 in the Daban et al.[306,310,327] and 1 in the NICE[321].

The RCT[303] conducted included 11 patients with epilepsy and found no statistical significance between the 2 study groups (high or low stimulation). The RCT of patients with depression was conducted by Rush et al.[306] and, as mentioned above, the HRSD scale scores showed no significant differences between either group (VNS or sham) although there were differences in the IDS scale. RCT 1+

The remaining uncontrolled studies included 492 patients with depression (except for 1 RCT[306] and 2 for epilepsy[304,330]). The effect size for the level of depression was significant in favour of VNS for a random effects model, with an average technique duration of 34 weeks. The heterogeneity test between studies showed a high statistical significance. Restricting the analysis to patients with depression refractory to standard treatment, the overall effect size was greater than with all the patients, with a heterogeneity test of 84%. The response rate was evaluated in 6 studies, and was 31.8% for a random effects model and with an average technique duration of 20 weeks. The heterogeneity test obtained a value of 66%. The response rate was 33.5% and heterogeneity 70%[309] in patients with depression refractory to standard treatment. Meta-analysis 1+

Regarding safety outcomes, the RCT of patients with depression306 had 3 losses: 1 due to suicide, 1 due to device explant because of infection and the third for hoarseness. Other side effects observed were voice alterations (30%), cough or hoarseness (20%), dyspnoea (9%), dysphagia (10%), neck pain (11%), paraesthesia (6%), vomiting (6%), laryngeal affectation (9%), dyspepsia (5%), wound infection (6%) and palpitations (2%). RCT 1+

Of the 12 uncontrolled studies, only 6 provided safety data. The serious adverse effects were: Case series 3

– Suicide or attempted suicide: cumulative incidence of 4.6% (or 0.090 suicides or suicide attempts per 100 patient/weeks during the intervention period).

– Mania or hypomania: cumulative incidence of 2.7% (0.094 cases per 100 patient/weeks).

– Hospitalisation due to worsening depression: cumulative incidence of 12.1% (0.225 cases per 100 patient/weeks).

Other short-term adverse effects were voice alteration (67.3%), cough (23%), incision site pain (19%), pain (16%), neck pain (15.5%), dyspnoea (15.2%), dysphagia (13.2%), headache (12%), pharyngitis (11.6%), chest pain (11%) and infection (5.6%).

Evidence summary

1+ **3**	The only RCT[306] in a systematic review[308] of 18 studies found no significant differences in the HRSD scale scores between the group receiving VNS and the sham group. Observational studies describe response rates of 40%[312] and 9%[313] and of short-term response and remission rates of 30%/15%[307], 40%/17%[310] and 57%/29%[311], respectively. There were also significant improvements in the HRDS scale score[311,316,317] and in the HRDS and IDS[313], compared to baseline. At 12 months, response and remission rates of 46%/29%[305] and 58%/36%[314], respectively, were observed. Other authors found a response rate of 27% in the group receiving VNS and 13% in the standard therapy group[315]. In general, the adverse effects described in the studies were similar, mild and limited in time. One study[307] found major or clinically relevant side effects in 17% of patients.
1+	One RCT found a response rate to VNS at 2 years of 33% in patients with unipolar depression and 38% in patients with bipolar disorder[320].
3 **2+**	A case series found that 77% of patients with early response maintained the response after VNS treatment at 24 months of follow-up[323]. At 12 months follow-up, a significant improvement in the HRSD scale score was observed compared to baseline, with 55% of patients responding at the time[324]. A non-randomised controlled study observed a significant decrease in the number of psychiatric consultations in the group receiving VNS, compared to the group undergoing drug therapy and psychotherapy at 12 months of follow-up[321].
1+	A RCT conducted in patients with epilepsy and depression found no statistical significant difference between the 2 study groups (high or low stimulation VNS)[303].
1+	A meta-analysis of uncontrolled studies observed a moderate effect size on the intensity of depression in favour of VNS, with an average technique duration of 34 weeks, but with high heterogeneity between studies. The response rate was 31.8%, with an average technique duration of 20 weeks[309].

1+	Regarding safety outcomes, a RCT found voice alterations (30%), cough or hoarseness (20%), dyspnoea (9%), dysphagia (10%), neck pain (11%), paraesthesias (6%), vomiting (6%), laryngeal affectation (9%), dyspepsia (5%), wound infection (6%) and palpitations (2%). There were 3 losses in this study: 1 due to suicide, another due to device explant caused by infection and the third due to hoarseness[306].
3	In addition, cases of suicide, attempted suicide, manic episodes, dyspnoea, worsening depression and suicidal pain have been seen. The most common adverse events were coughing and voice alteration[324].

Recommendations

√	The use of vagus nerve stimulation outside the scope of research is discouraged due to the invasive nature of the procedure, uncertainty about its efficacy and adverse effects.

8.5 Transcranial magnetic stimulation as adjunctive treatment for resistant depression

Key question

- What is the safety and efficacy of transcranial magnetic stimulation as adjunctive treatment for resistant depression?

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a non-invasive technique whereby a strong magnetic field stimulates the cerebral cortex to selectively depolarise it.

TMS can be a single pulse, as used in research to locate brain functions, or as a series of repetitive regular pulses (rTMS) for therapeutic purposes. In turn, repetitive TMS can be applied at relatively low frequencies, by applying a stimulus every second or less (slow or low frequency rTMS) or by applying more than 20 stimuli per second (fast or high frequency rTMS). The modulatory effects on cortical excitability are different, with low frequency having an inhibitory effect, and fast having an activating effect[13].

The initial application of rTMS was driven by functional neuroimaging data that showed reduced activity in the left prefrontal cortex in patients with depression. More recently, various researches have postulated the existence of an imbalance in the activity of the frontal lobes (hypoactivity in the left frontal lobe and excessive inhibitory activity in the right frontal lobe), which has led to the use of a combination of low frequency rTMS (suppression) in the right prefrontal cortex and high frequency rTMS on the left.

TMS is a non-invasive technique, usually performed safely as an outpatient procedure. Although there is variability in the protocols, TMS sessions are usually performed by a trained technician and last between 30 and 60 minutes. The usual regime is 5 weekly sessions for a period of 4-5 weeks (20-30 sessions in total).

8.5.1 Transcranial magnetic stimulation in the treatment of depression

Transcranial magnetic stimulation has been studied as a treatment for depression, and been compared with sham TMS in a significant number of RCTs; of which 3 meta-analyses and a systematic review are described below.

A Cochrane review was published by Rodriguez-Martin et al.[332] in 2002, which included 16 RCTs (7 of them for drug treatment-resistant depression), of which 14 were part of a meta-analysis. Compared with sham TMS, rTMS obtained better Beck depression and Hamilton scale scores after 2 weeks of treatment (applied to the left prefrontal cortex with high frequency); this difference was not present 2 weeks later. They also found rTMS was better (according to the Hamilton scale) when applied to the right prefrontal cortex at low frequency. The overall difference between the active and sham treatment was small, but statistically significant, so the authors concluded that there was not strong evidence to support the benefit of TMS as an antidepressant treatment.

Meta-analysis 1+

Herrmann et al.[333] published another meta-analysis of 33 RCTs in 2006 (of which 10 were in the Martin et al. meta-analysis), which included 475 patients undergoing rTMS and 402 with sham TMS. At baseline, the mean MADRS scale score was 27.05 and 25.86 in the active and sham groups, respectively, which corresponds to severe depression. In the group that received rTMS there was a 33.6% reduction in depressive symptoms (as measured by the HRSD and MADRS scales), while the reduction in the sham group was 17.4%; this was a clinically significant difference. However, there was great variability in the individual study results (evidence of significant heterogeneity in the meta-analysis).

Meta-analysis 1+

The *National Institute for Clinical Excellence* (NICE) [334] published a systematic review that included the previous Cochrane review[332], 7 randomised clinical trials[335-341] and a case series[342]. Potential adverse effects of the technique were scalp discomfort (0-41%), headache (10%), neck stiffness (3%), transient hearing loss (11%) and an isolated case of the induction of mania and seizures. The following NICE guideline13 considered that the existing evidence on transcranial magnetic stimulation for the treatment of severe major depression raised uncertainty about the clinical efficacy of the procedure. It thought it may depend on different factors, such as the intensity, frequency, bilateral application and/or treatment duration, and concluded that TMS should only be performed in research studies designed to investigate these factors.

SR 1+

Another meta-analysis published in 2010 by Slotema et al.[343] included 34 clinical trials in which TMS was compared with sham TMS in the treatment of severe major depression. Of these RCTs, 10 were in the Hermann and NICE reviews, 11 in the Hermann or NICE review only and 13 RCTs were new. The weighted average effect size of rTMS compared with sham treatment (using rating scale scores) was 0.55 ($P < 0.001$) in favour of rTMS. It was also observed that rTMS monotherapy was more effective than rTMS as an adjuvant treatment of antidepressant mediation and that electroconvulsive therapy (ECT) was superior to rTMS in the treatment of depression (effect size 0.47, $P = 0.004$). Despite these statistically significant differences, different authors criticised the methods used in the clinical trials[344-346]. For example, the TMS was applied to the left prefrontal cortex in over 90% of the cases, but the stimulation parameters were extremely variable and the severity of the patient symptoms was generally low: only 3 of the 34 studies included patients who had not responded to 2 or more antidepressants before their current episode.

Meta-analysis 1-

To try to resolve some of these issues, the American *National Institutes of Health* sponsored a multicentre study in which 199 patients with major depression (unipolar and non-psychotic) without drug treatment were randomized[347]. In this trial, rTMS parameters were standardised to maximise the likelihood of antidepressant effects (5 times per week with TMS at 10Hz, 120% of motor threshold, 3,000 pulses/session for 4-6 weeks) and key methodological limitations were avoided (e.g. adequacy of blinding, validity of simulated treatment, training of evaluators, result assessment reliability and MRI image adjustment for proper placement on the scalp). The results showed a significant difference in the proportion of remission (14.1% for rTMS vs 5.1% for sham TMS, p = 0.02), although the number was very low, with a number needed to treat of 12. It is worth noting that most patients with remission had low resistance to antidepressant drug treatment when starting the study, as in previous studies.

RCT 1+

8.5.2 Transcranial magnetic stimulation in treatment-resistant depression

Few studies have investigated the use of TMS in patients with treatment-resistant depression. In general, it is difficult to draw conclusions because of the small sample sizes, variability in the inclusion criteria and treatment regimens and high dropout rates; although overall the results were positive.

A double-blind, controlled trial[348] evaluated high-frequency rTMS in 45 drug-resistant patients with major depression (with at least 2 previous attempts with antidepressants other than tricyclics). The patients received 15 sessions of rTMS or sham TMS for 3 weeks in combination with 20mg of escitalopram. After the last TMS session, patients continued with 20mg of escitalopram for 9 weeks. After 3 weeks of treatment, a superior effect for rTMS (clinically and statistically) over sham TMS was shown, using the Hamilton scale. No side effects were observed.

RCT 1+

A final randomised, double-blind, controlled trial[349] evaluated the efficacy of repetitive transcranial magnetic stimulation, either unilateral or bilateral, in the treatment of resistant major depression. A total of 74 patients aged between 18 and 85 years and more than 21 points on the Hamilton scale were randomised to receive unilateral, bilateral rTMS or sham TMS. After randomisation, it was noted that 6 patients had failed in a previous ECT treatment, so they were excluded, as they had a more severe and resistant depression which would probably not have responded to the TMS. The remission rate (HRSD ≤ 10) differed significantly between the 3 treatment groups: 34.6% bilateral, 4.5% unilateral and 5.0% simulated. The remission rate was significantly higher in the bilateral group than the sham and unilateral TMS groups, while the remission rate in the unilateral group was similar to the sham TMS group.

RCT 1+

Efficacy for the technique with no significant side effects was found in 3 open label studies[350-352] of small sample size (between 11 and 21 patients).

Case series, 3

8.5.3 Comparison of transcranial magnetic stimulation with electroconvulsive therapy

Berlim et al.[353] conducted a systematic review and meta-analysis of RCTs comparing transcranial magnetic stimulation with electroconvulsive therapy in patients with major depression. The authors included 7 studies[354-360] with a total of 294 patients with major depression who were randomised to TMS or ECT, with an average of 15.2 ± 4 and 8.2 ± 2 sessions, respectively. The remission rate at the study end was 33.6% of patients in the TMS group and 52% of those having ECT, which was a statistically significant difference. The calculated NNT was 6, meaning that 1 in 6 patients reached remission using ECT instead of TMS. The variability did not exceed that expected by chance and the risk of publication bias was low. The changes in depressive symptoms (measured with the MADRS and Hamilton scales) indicated a significant difference in favour of ECT. There were no differences in drop-out rates observed. A subgroup analysis in which RCTs included mixed samples of patients with major depression with and without psychotic symptoms showed a greater size effect for remission and changes in depressive symptoms than studies that included patients with psychotic symptoms only. The sample size was small, between 26 and 75 patients. The main criticisms, common to all studies, was the use of low energy and frequency for both the ECT and the TMS, even in patients with psychotic symptoms; as well as not adequately describing the masking techniques. Despite these limitations, the meta-analysis showed that ECT is significantly more effective than TMS in the treatment of major depression, particularly for those patients with severe depression, psychotic features and a high degree of resistance to treatment.

Meta-analysis, 1 +

Evidence summary

1+	A systematic review comparing sham TMS with rTMS in patients with major depression and resistant major depression found better BDI and HRSD scale scores for rTMS after 2 weeks of treatment, although this difference was not present 2 weeks later. These differences were small but statistically significant[332].
1+	There was a reduction in depressive symptoms (using the HRSD and MADRS scales) of 34% for rTMS compared with 17% for the sham group in patients with severe depression. Although the effect was clinically significant, the results were very variable[333].
1+	A systematic review concluded that there was uncertainty about the clinical efficacy of rTMS in severe major depression, which may depend on factors such as intensity, frequency, bilateral application and/or duration of treatment. Adverse effects were generally mild[334].
1+	Another meta-analysis included 34 clinical trials comparing rTMS with sham TMS in the treatment of patients with severe depression. The weighted average effect size of rTMS (rating scale scores) compared with the sham treatment was 0.55 (P <0.001) in favour of rTMS. It was also observed that rTMS monotherapy was more effective than rTMS as adjunctive treatment to antidepressant medication, and that electroconvulsive therapy was superior to rTMS in the treatment of depression[343].

1+	The results of a multicentre study by the American National Institutes of Health showed a very low but statistically significant difference between rTMS and sham TMS in the remission rate. As in previous studies, most of the patients with remission had low resistance to antidepressant drug treatment at the time of starting the study[347].
1+	There was a superior effect (clinically and statistically) for rTMS over sham TMS according to the Hamilton scale in patients with drug-resistant major depression, with no observed side effects[348].
1+	The remission rate was significantly higher for bilateral rTMS (35%) than for unilateral or sham (5%) in patients with resistant major depression[349].
1+	A systematic review and meta-analysis of 7 RCTs compared TMS with electroconvulsive therapy in patients with major depression. The remission rate at the end of the study was 34% for the TMS group and 52% for the ECT group, with a positive significant difference for ECT. Changes in depressive symptoms (measured using the MADRS and Hamilton scales) were also significantly favourable towards ECT, with no difference in the drop-out rate. In summary, ECT is significantly more effective than the TMS for the treatment of major depression, particularly in patients with severe depression, psychotic symptoms and high treatment resistance[353].

Recommendations

B	Transcranial magnetic stimulation is not currently recommended as a treatment for depression, due to uncertainty about its clinical efficacy.

9. Other treatments

9.1 Exercise

Key question

- Is physical exercise effective in patients with depression?

Exercise is known to improve mood and a sense of wellbeing, so we have attempted to determine to what extent it may be useful in treating patients with depression.

Several explanations have been proposed for its influence on depression. In the developed world, regular exercise is seen as something positive, so that the patient with depression can get positive feedback and increased self-esteem when doing it. In addition, exercise can improve social contact and facilitate the support of others. In addition, physical activity produces physiological effects such as changes in the concentrations of endorphins and monoamines, thus improving subjective welfare[361].

For the purposes of this guide, exercise has been defined as a physical activity used in the treatment of depression that is characterised as achievable, structured and can be undertaken individually or in groups. It can be divided into aerobic forms (training of cardio-respiratory capacity) and anaerobic forms (training for muscular strength, endurance, flexibility, coordination and relaxation)[362].

Aerobic forms of exercise, especially jogging or running, are the most investigated in clinical trials. As well as the type of exercise, its frequency, duration and intensity should be described. Among the most significant limitations of some of the studies are the inclusion of voluntary patients, who may be more motivated[363], and studies conducted outside the clinical setting, which makes it difficult to assess the efficacy of its prescription in normal practice[364].

Effectiveness of exercise

As part of the NICE depression guideline (2009)[13], a systematic review was conducted about the likelihood of remission and symptom reduction in patients diagnosed with depression who exercised compared with not exercising and with different treatments (pharmacological, psychotherapeutic, social support and meditation). It included 25 trials, of which 9 were included in the previous 2004 version of the guideline. Data from nearly 2000 participants are provided.

The conclusions reflected in the NICE guideline[13] were that structured and supervised exercise, especially group physical activity, may be an effective intervention in improving depressive symptoms for depressed patients, particularly those diagnosed with mild to moderate depressive disorder. Although no evidence of benefits was found among different types of exercise, patient preference could be the determining factor. This guideline recommended the implementation of structured and supervised exercise programmes (3 times a week for 45-60 minutes) over 10-14 weeks for people with mild to moderate depression. SR 1+

Subsequently, the *Scottish Intercollegiate Guidelines Network* (SIGN) guideline on the non-pharmacological management of depression also recommended exercise programmes as a treatment option for depression, while emphasising the recommendation of exercise for motivated patients only[363]. SR 1+

In 2012, the WHO considered the promotion of physical activity as a treatment for adults with depressive episodes and a sedentary lifestyle. In moderate and severe depression, physical activity should be considered as an adjunct to antidepressants or brief, structured psychotherapy[365]. SR 1+

The following systematic reviews and meta-analyses were located and updated by our group: Silveira et al.[366], Josefsson et al.[367], Danielsson et al.[368], Bridle et al.[369] (in patients over 65 years), Mammen and Faulkner[370] and Cooney et al.[364]. In general, the exercise programmes used were of relatively high frequency (at least 3 times per week), and lasted 45-60 minutes over periods of 10-12 weeks.

In the meta-analysis published by Silveira et al.[366], 10 clinical trials were selected, 3 of which were included in the NICE guideline[13] review. Physical exercise, especially aerobic, statistically significantly improved depressive symptoms. However, the effectiveness of exercise in the treatment of depression was influenced by variables such as age and severity of symptoms. Subgroups of patients older than 60 years and those with mild depressive disorder showed a better response to exercise than other age groups or patients with a greater severity of depressive symptoms. Meta-analysis 1+

Joseffson et al.[367] analysed [13] studies in which a statistically significant positive effect for exercise on depressive symptoms was observed. Although only 2 of these studies were of high methodological quality[371,372], when they were evaluated separately, they maintained their statistical significance, although the effect size was smaller. They concluded that physical exercise can be recommended to patients with a mild-moderate degree of depression. They also noted that it may not be appropriate for all patients with depression, so it has to be recommended to those who are sufficiently motivated and physically fit to continue the programmes. Meta-analysis 1+

Danielsson et al.[368] selected 14 studies, 9 of which were of high methodological quality, in their systematic review with 1,139 patients. The aim was to analyse the quality of the evidence in the treatment of patients with major depression in 3 types of studies: aerobic exercise vs antidepressants, aerobic exercise vs any physical activity and aerobic exercise as an enhancement to standard therapy vs standard therapy. There were 3 studies evaluated but not included in previous reviews: Hoffman et al.[373], Mota-Pereira et al.[374] and Trivedi et al.[375.] This review concluded that aerobic exercise seems to improve depression when used in combination with the drug treatment, although further studies to evaluate other physical exercise are necessary, as in any study evaluated, aerobic exercise had similar results to other non-aerobic physical activities, such as relaxation. Meta-analysis 1+

In the over-60s, Bridle et al.[369] reviewed 9 clinical trials with 667 participants which evaluated the effect of exercise on depressive symptoms. They found a small but statistically significant reduction in depressive symptoms in this population, with a structured, mixed programme of aerobic and non-aerobic exercise tailored to individual capabilities.

Meta-analysis 1+

Mammen and Faulkner[370] conducted a systematic review of prospective studies whose objective was to determine whether aerobic exercise could prevent future episodes of depression. There were 30 studies included in the analysis, 25 of which showed evidence that even low levels of physical activity (walking less than 150 minutes/week) could prevent a future depressive episode.

SR of different study types 2++, 2+

The latest Cochrane review on the effect of exercise on depression[364] found moderate evidence of efficacy in reducing depressive symptoms compared with no intervention. In the 7 studies comparing exercise with psychotherapy and the 4 comparing it with pharmacotherapy, exercise appears to be less effective than the comparison treatments. There is no conclusive evidence on the type and intensity of exercise or the optimal frequency and duration, and few quality studies have evaluated the role of prescribed exercise in routine clinical practice. The authors recommend further studies to determine what type of exercise is most effective in patients with depression, whether exercise is as effective as antidepressants or psychotherapy, and whether the benefits can be maintained long term.

Meta-analysis 1+

Evidence summary

1+	The NICE guideline recommended a programme of structured and supervised exercise (30-60 minutes, 3 times a week for at least 10-12 weeks) for patients with major mild to moderate depression as an intervention with potentially clinically significant impact on depressive symptoms[13].
1+	The SIGN guideline recommended structured exercise programmes as a treatment option in patients with depression, while emphasising it should be for motivated patients only[363].
1+	The WHO advises the promotion of physical activity as part of the treatment in adults with a depressive episode and sedentary lifestyle. In moderate and severe depression, physical activity should be considered as an adjunct to antidepressants or brief, structured psychotherapy[365].
1+	Exercise, especially aerobic, statistically significantly improved depressive symptoms. Subgroups of patients older than 60 years and those with mild depressive disorder showed a better response to exercise than other age groups or patients with greater severity of depressive symptoms[366].
1+	Aerobic exercise appears to improve depression when used in combination with drug therapy[368].
1+	There is no conclusive evidence for the effectiveness of aerobic exercise over other types of physical activity; while, in some studies, exercise obtained similar results to other activities such as relaxation[13,368]. In addition, it may not be appropriate for all patients with depression, so it should be recommended to those who are sufficiently motivated and physically fit enough to continue the programmes[13,363,368].

1+	A Cochrane review on the effect of exercise on depression found moderate evidence of efficacy in reducing depressive symptoms compared with no intervention. It seems to be less effective when compared with psychotherapy or pharmacological treatment. There is no conclusive evidence on the type and intensity of exercise, or the optimal duration and frequency. There are few quality studies evaluating the role of prescribed exercise in normal clinical practice[364].
2+	There is no conclusive evidence on the utility of exercise as an intervention in the maintenance and prevention of relapse, although it seems that aerobic exercise may prevent future episodes of depression[370].

Recommendations

B	Patients with depression are strongly encouraged to perform physical exercise as a healthy living habit. It is imperative that the patient is motivated and willing to do exercise, according to their physical condition and tailored to their individual preferences.
B	Physical activity should be considered an adjunct to antidepressants and/or psychotherapy in severe and moderate depression.

9.2 St. John's Wort

Key question

- What is the safety and efficacy of St. John's wort in the treatment of adult depression

St. John's wort (Hypericum perforatum) is a plant with a rigid stem and yellow flowers that has been used since ancient times in traditional medicine as an astringent, antiseptic and healing agent when applied externally, and as a treatment for sleeping disorders, depression and anxiety when taken orally[376.] Its mechanism of action is not fully established and Hypericum perforatum extracts contain at least 10 pharmacologically active constituents (hypericin, flavonoids, xanthones and bioflavonoids) which could act in different ways: by weakly inhibiting MAO A and B[377], selectively inhibiting serotonin reuptake[378] or reducing the expression of interleukin 6[379].

In general, the amount and proportions of components in herbal preparations can vary, so that different preparations of St. John's wort (SJW) or even different batches of the same brand may not be therapeutically equivalent. Furthermore, although St. John's wort is usually prepared in a standardised manner with respect to the amount of hypericin, it is not known if this is the effective dose or even if it is the only active ingredient.

The studies included in this review used different extracts of SJW, with the most frequent being LI 160, which contains 0.72-0.96 mg of hypericin. However, other studies used different extracts, such as WS 5570, WS 5572, WS 5573, STEI300, ZE 117, Psychotonin, esberico, Lo-Hyp-57, Calmigen and STW3, and several of them did not establish the hypericin content.

Safety, efficacy and effectiveness of St. John's wort

4 systematic reviews[13,380-382] are included, with the most important being the Cochrane Collaboration with 29 RCTs included[380.] A follow-up study of a previous RCT[383,] an open-label multicentre study[384] design and an observational study[385] were also included, which were not included in previous reviews.

The Cochrane review included 29 RCTs[380] (5,489 patients) comparing SJW with placebo (n = 12), other antidepressants (n = 11) or both (n = 6). There were 19 studies conducted in patients with mild to moderate depression, and 9 with moderate to severe. A wide variety of Hypericum preparations were used in the studies, with the daily dose of extract varying between 240-1800 mg, although in most studies it was between 500-1200 mg. Antidepressants used as active comparators were fluoxetine (6 studies, doses of 20-40 mg), sertraline (4 studies, 50-100 mg), imipramine (3 studies, 100-150 mg), citalopram (1 study, 20mg) and paroxetine (1 study, 20-40 mg). The meta-analysis with 18 studies comparing SJW with placebo showed high variability. Thus, the 9 RCTs with larger sample sizes showed a probability of response to SJW less than the 9 studies with small sample size (RR 1.28 and 1.87, respectively), when compared with placebo. The probability of response to SJW was similar to standard antidepressants (RR 1.02 for tricyclic and tetracyclic antidepressants and 1.00 with SSRIs). In general, RCTs conducted in German-speaking countries were more favourable to SJW. Finally, withdrawal due to adverse effects was less frequent in patients who took SJW than those taking first-generation antidepressants or SSRIs. SR 1+

The NICE guideline[13] included 19 RCTs (3,149 patients) comparing St John's wort (SJW) with placebo, other antidepressants, or both; and of those, 16 had been already included in the Cochrane review[380]. In all studies, participants had moderate to severe depression and only in 1 study were participants older than 60 years of age. The NICE guideline included 10 studies with a total of 1,520 participants compared with placebo. The results show that the SJW is more effective than placebo in achieving response, both in moderate and severe depression. However, the results were not sufficient to assess remission. It was also observed to be more effective than placebo in reducing symptoms in moderate depression. No differences were observed between SJW and placebo regarding the likelihood of abandoning treatment early for any reason or for information about adverse effects. There were 11 comparative studies (n = 1,629) against other antidepressants included: TCAs (4 studies), maprotiline (1 study) and SSRIs (6 studies). Overall, there were no differences observed between SJW and other antidepressants in the response or remission rate or in reducing depression symptoms. The only differences were that the SJW performed better in achieving a response in moderate depression, while it was less effective than low doses of antidepressants for severe depression. SJW showed better tolerability than antidepressants, particularly TCAs, as patients were less likely to abandon treatment early due to adverse effects. SR 1+

Rahimi et al.[381] conducted a systematic review and meta-analysis of [13] RCTs comparing SJW with SSRI antidepressants. There were 6 studies of patients with mild to moderate depression, 2 with moderate, 2 with moderate to severe depression and 3 with different levels of severity. Except for a low quality study[386], the rest were included in the Cochrane review[380]. The minimum effective doses of antidepressants were used, while there was a high variability in the SJW dose, so the findings should be considered with caution. There were no significant differences in response or remission rates or in HRSD scale score reduction between SJW and SSRIs. Drop-out due to adverse effects was significantly lower for SJW than SSRIs. SR 1+

Carpenter[382] conducted a systematic review that included 17 randomised studies, 15 of which were included in the Cochrane review[380] and only 2 added[387,388]. All studies were conducted on patients with moderate to severe depression and 6 of them had comparisons with an active treatment (fluoxetine, citalopram, sertraline or imipramine). Of the 17 studies, 10 obtained results significantly in favour of SJW over placebo, which were all in patients with mild to moderate depression. The effect size varied widely, with an average of 0.64, which by convention is defined as moderate to large. Of the 7 studies with negative results, 5 were in patients with mild to moderate depression and 2 in people with moderate to severe depression. No differences between SJW and active treatments were observed.

SR 1+

Sarris et al.[383] evaluated [340] adult patients with major depression and a baseline Hamilton Rating Scale (HRSD) score of at least 20 points in the *Hypericum Depression Trial Study Group*[389]. The patients were randomised to receive SJW, placebo or sertraline (50-100 mg) for 8 weeks, and at the end of treatment there were no significant differences between groups regarding HRSD scale scores or response rate. In this study, 124 patients who responded well to treatment in the first 8 weeks were randomised to SJW, sertraline or placebo groups. At week 26, the Hamilton Rating Scale (HRSD) score was similar for SJW, sertraline and placebo, with significantly improved scores for the assessment at 8 weeks. The authors considered that SJW and sertraline were effective therapeutically, although the pronounced placebo effect prevented a significant result between it and the active treatments.

RCT 1+

A multicentre, open-label study not included in previous reviews[384] primarily assessed the safety of SJW used to treat 440 outpatients with mild to moderate depression. Almost half, 217 (49%), reported 504 adverse events, of which 30 (6%) were related to treatment, with the most common affecting the digestive system and skin. Mean scores on the HRSD and CGI scales, respectively, fell from 20.58 and 3.99 points at baseline to 12.07 and 2.20 points at week 26 and 11.18 and 2.19 at week 52.

Open label study, 3

Finally, an observational study in Germany[385] of 1,778 adult patients with 'depressive syndrome' were treated with a SJW extract for 12 weeks, after which the score on the ICD-10 symptom scale decreased by 63% and the proportion of patients described as normal or mildly ill (CGI-s) increased from 22% at baseline to 72%. Finally, better results were associated with younger age and a shorter duration of depressive disorder.

Case series, 3

Evidence summary

1+	Information available from randomised trials shows that St. John's wort is superior to placebo in the short term for achieving response in patients with mild to moderate major depression, and its efficacy is similar when compared with both tricyclic and SSRI antidepressant drugs. However, a limiting factor in the analysis of these studies was the use of different SJW extracts, with variable contents of active ingredients and minimum effective doses of antidepressants[13,380-382].
1+	SJW has fewer side effects than standard antidepressants, particularly TCAs, and is less likely to lead to early treatment drop-out due to adverse effects[13,380-382].

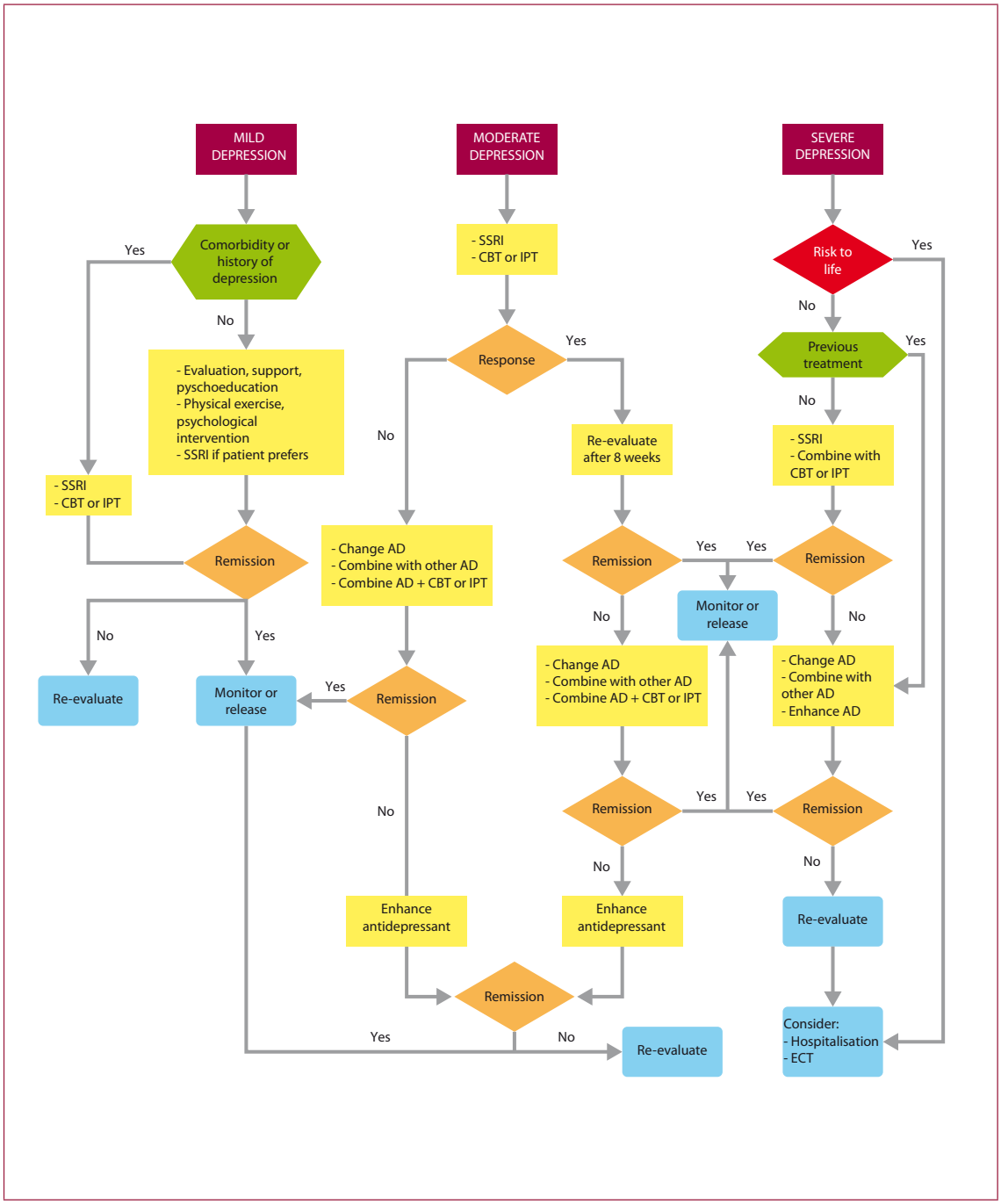
1+	A 26-week study showed no differences in the Hamilton scale score for groups receiving SJW, sertraline (50-100 mg) or placebo[383].
3	A multicentre, open-label study reported 6% of adverse effects associated with SJW, with low HRSD and CGI scale scores, after both 26 and 52 weeks of treatment[384].
3	An observational study of patients with 'depressive syndrome' treated with SJW extract for 12 weeks showed a 63% decrease in the ICD-10 scale symptom score, with the percentage of patients described as normal or mildly ill (GCI-s) as 72%[385].

Recommendations

B	Although there is evidence of the efficacy of St. John's Wort in the treatment of mild to moderate depression, its use is not recommended for the following reasons: - Ignorance of the active ingredients, mechanisms of action and persistence of the antidepressant effect. - A lack of standardisation of the dose. - The variability of different commercial preparations, which may have different amounts and proportions of its components and may not be therapeutically equivalent.
B	Healthcare professionals should inform patients taking St. John's wort of its serious potential interactions with some drugs, some of which are commonly used, such as oral contraceptives.

10. Diagnostic and therapeutic strategies

The diagnosis and treatment algorithm for major depression in adults is shown immediately below, with detailed information about it on the following pages.



AD: Antidepressant
SSRI Selective serotonin reuptake inhibitors
ECT: Electroconvulsive therapy
CBT: Cognitive behavioural therapy
IPT: Interpersonal therapy

Algorithm notes

1. General

- The treatment of depression in adults should be comprehensive and cover all psychotherapeutic, psychosocial and pharmacological interventions that can improve well-being and functional capacity.
- It is recommended that the management of depression in adults is performed following a stepped care model, so that interventions and treatments intensify according to the condition and evolution of the patient.
- The management of depression should include:
  - Psychoeducation
  - Individual and family support
  - Coordination with other professionals
  - Attention to comorbidity
  - Regular monitoring of mental state

2. The stepped care model in the treatment of depression

To implement the stepped care model of treatment, 3 levels of treatment should be established:

1. The first level treatment will address mild depression, based primarily on psychoeducation, support, exercise and psychological interventions.

2. The second level of treatment aims to moderate depression, and is mainly based on the drug treatment or psychological interventions.

3. The third level is that of severe or resistant depression, in which the main treatments are combined (psychotherapy + antidepressant) and/or pharmacological strategies in resistant depression. When these options are not effective, hospitalisation and electro-convulsive therapy should be assessed.

3. Assessment of severity and monitoring response to treatment plan

Evaluation will be based primarily on the clinical interview, although the use of assessment instruments can provide additional information.

The severity of the episode depends on the following criteria:

- Duration, number and intensity of symptoms.
- Inadequate response to treatment.
- Comorbidity.
- Personal history of depression.
- Suicidal ideation or suicidal behaviour, psychotic symptoms, low social support, disability.

The frequency of symptom assessment and monitoring should be performed according to the severity, comorbidity, cooperation with treatment, social support and frequency

and severity of side effects from the treatment prescribed.

It is recommended that all patients with moderate depression treated with drugs are assessed again 2 weeks after initiating treatment, and within 8 days if it is a case of severe depression. Patients with drug therapy must be closely monitored, at least for the first 4 weeks.

The acute phase of treatment is considered as the first 8-12 weeks, in which the objective is remission of symptoms and recovery of functionality. The maintenance phase then lasts for 6-24 months in which previous functioning should be restored and recurrence prevented.

Each review will assess the response, treatment adherence, side effects and risk of suicide.

4. Referral from primary care

The decision to refer from primary care for another approach should follow the severity criteria previously described and when the following exists:

- Risk of suicide or aggression towards others
- Severe depressive episode with psychotic symptoms
- Suspected bipolarity
- Highly recurrent moderate depression
- Prolonged depressive episodes
- Substance abuse
- Denial of disorder
- After 2 or more failed treatment attempts
- When symptoms raise diagnostic or therapeutic doubts

The type of such referral (urgent, preferred or ordinary) will be according to the overall assessment of these criteria, the patient's symptoms and possible care period.

The referral will be **urgent** in the following situations:

- A major depressive episode with psychotic symptoms
- High suicide risk (recent serious suicidal behaviour, suicide plan prepared, expression of suicidal intent confirmed at the end of the interview, social and family risk or lack of support)

The derivation will be **preferred** in the following situations:

- Suspected bipolarity and/or risk of suicide (suicidal ideation without any of the above criteria and relief after the interview, intention to control suicidal impulses, acceptance of treatment, containment measures agreed and effective social and family support)

In all cases, the reasons for the referral should be recorded in the medical record.

11. Quality indicators

Key question

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

Once the recommendations are formulated, it is important to know whether the expected objectives will be reached after implementation. Thus, different variables related to the care process and the most relevant clinical outcomes must be evaluated.

In assessing the clinical management of depression, it is recommended to measure the 3 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 within the scope of different health areas.

The proposed 5 indicators are listed and described below. They are quantitative measures that can be used as a guide and to analyse evolution over time if obtained on a regular basis, i.e. they can be used for monitoring.

Proposed indicators:

Area	Assessment focus	Indicator
Diagnosis	Process	Under- or overdiagnosis of depression
Treatment	Process	Monitoring treatment with antidepressants
Treatment	Result	Maintenance of treatment with antidepressants
Treatment	Process	Efficient use of antidepressants
Treatment	Process	Combined therapy in major depression
Treatment	Process	Psychotherapeutic treatment in mild-moderate depression

Quality dimensions addressed:

Quality dimension	Indicator
Diagnostic effectiveness	Under- or overdiagnosis of depression
Therapeutic effectiveness	Monitoring treatment with antidepressants
Therapeutic effectiveness	Maintenance of treatment with antidepressants
Therapeutic effectiveness	Efficient use of antidepressants
Therapeutic effectiveness	Combined therapy in major depression
Therapeutic effectiveness	Psychotherapeutic treatment in mild-moderate depression

Indicator	Under- or overdiagnosis of depression
Justification	It is estimated that 28% of patients with depression are not diagnosed, although this could be lower in more severe forms of depression. On the other hand, over-diagnosis of depression has also been revealed as a major problem. This indicator provides information about a possible under- or over-diagnosis of depressive episodes.
Formula	Number of adult patients with recorded diagnosis of depression ---------- x 100 No. of adult patients expected to suffer depression, according to epidemiological study estimates
Description of terms	Adult patients: Patients over 18 years. Recorded diagnosis of depression: Written record of the diagnosis in the Clinical Record that the patient suffered a major depressive disorder episode in the reference period (prevalent cases). Patient Medical History: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. Epidemiological studies: To estimate the number of expected cases, the best quality epidemiological study available that has been performed on populations with the greatest sociodemographic similarity will be selected. The expected number of patients will be obtained based on standardised estimates of age and sex.
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes adult patients diagnosed in the geographic area in the reference period.
Exclusion criteria	Patients younger than 18 years, patients not residing in the geographic area of study and those who have not had an active episode in the study period, despite having a recorded history of diagnosis of major depression.
Indicator Type	Process
Data sources	Patient clinical history, epidemiological studies.

Indicator	Monitoring treatment with antidepressants
Justification	The continued treatment of depression with antidepressants for 6 months or more helps to consolidate treatment response and reduces the risk of relapse. To reduce the number of patients not adequately completing the treatment period, it is recommended to maintain contact with them. This indicator allows monitoring of treatment with antidepressants.
Formula	Number of adult patients with a recorded diagnosis of depression with a follow-up contact within 1 month of the indication of treatment with antidepressant drugs - x 100 Number of adult patients with recorded diagnosis of depression who were indicated antidepressant medication
Description of terms	<u>Adult patients</u>: Patients over 18 years. <u>Indication of treatment with antidepressant drugs</u>: Record of antidepressant drug treatment after diagnosis of a major depressive disorder episode. New episodes of patients with prior history of major depressive disorder will also be counted. The indication must be made during the reference period. <u>Patient Medical History</u>: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. <u>Monitoring Contact</u>: A patient can make a follow-up contact by a medical consultation or by another system, provided this has been recommended and agreed in advance by the physician.
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes adult patients diagnosed in the geographic area in the reference period.
Exclusion criteria	Patients younger than 18 years, patients not residing in the geographic area of study, transfers to other areas, deaths, withdrawal of medication by physician and diagnosis date of less than 6 months.
Indicator Type	Result
Data sources	Patient clinical history.

Indicator	Maintenance of treatment with antidepressants
Justification	The continued treatment of depression with antidepressants for 6 months or more helps to consolidate treatment response and reduces the risk of relapse. This indicator allows monitoring of treatment with antidepressants.
Formula	Number of adult patients with a recorded diagnosis of depression who maintain treatment with antidepressant drugs for 6 months ---------- x 100 Number of adult patients with recorded diagnosis of depression who were indicated antidepressant medication
Description of terms	Adult patients: Patients over 18 years. Indication of treatment with antidepressant drugs: Record of antidepressant drug treatment after diagnosis of a major depressive disorder episode. New episodes of patients with prior history of major depressive disorder will also be counted. The indication must be made during the reference period. Patient Medical History: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. Reference period: Generally the last 12 months, but includes all adult patients diagnosed in the geographic area. Geographical Area: The geographic reference area for the population residing there who are diagnosed with major depressive disorder. Indication of treatment: All new indications for pharmacological treatment with antidepressants made during the reference period will be included. Maintenance treatment: A patient is deemed to have performed maintenance treatment for 6 months which was appropriate, if this is stated in the Medical History.
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes adult patients diagnosed in the geographic area in the reference period who have been indicated to start treatment with antidepressant drugs.
Exclusion criteria	Patients younger than 18 years, patients not residing in the geographic area of study, transfers to other areas, deaths, withdrawal of medication by physician and diagnosis date of less than 6 months.
Indicator Type	Result
Data sources	Patient clinical history.

Indicator	Efficient use of antidepressants
Justification	SSRIs are better tolerated and safer than other antidepressants. New dual drugs, serotonin and norepinephrine reuptake inhibitors, are no more effective, although more expensive and can potentially have more side effects. This indicator is to monitor the efficient use of antidepressants.
Formula	Number of adult patients with a recorded diagnosis of depression who are treated with SSRIs as first choice ---------- x 100 Number of adult patients with recorded diagnosis of depression who were indicated antidepressant medication
Description of terms	Adult patients: Patients over 18 years with recorded diagnosis of depression and start of indication of treatment with antidepressants during the reference period will be counted. Recorded diagnosis of depression: Written record of the diagnosis in the patient Medical History that a new diagnosis of depressive disorder was made in the reference period. New episodes of patients with a history of depressive disorder will also be counted. Patient Medical History: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. Indication of treatment: All new indications for pharmacological treatment with antidepressants made during the reference period will be included. Indication of treatment with SSRI drugs as first choice: It is considered that a patient has been prescribed a SSRI as first choice if this is stated in the medical history
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes adult patients diagnosed in the geographic area in the reference period who have been indicated to start treatment with antidepressant drugs.
Exclusion criteria	Patients younger than 18 years and those not residing in the geographic area of study.
Indicator Type	Process
Data sources	Patient clinical history.

Indicator	Combined therapy in major depression
Justification	Some psychotherapeutic treatments have been shown to play a significant role in the treatment of depression. The combination of antidepressants and psychotherapy is considered the most effective option for severe depression. This indicator is to monitor the coverage of psychotherapeutic treatment in combination with pharmacological treatment in severe depression.
Formula	Number of adult patients with a recorded diagnosis of severe depression treated with psychotherapy in combination with antidepressants - x 100 Number of adult patients with recorded diagnosis of severe depression
Description of terms	Patients with combined treatment of antidepressants and psychotherapy: The patient receives both simultaneously and in a coordinated manner from professionals providing them. Patients treated with psychotherapy: Those receiving any of the duly validated treatments. Adult patients: Patients over 18 years with recorded diagnosis of depression and start of indication of treatment with antidepressants during the reference period will be counted. Recorded diagnosis of depression: Written record of the diagnosis in the patient Medical History that a new diagnosis of depressive disorder was made in the reference period. New episodes of patients with a history of depressive disorder will also be counted. Patient Medical History: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. Indication of treatment: All new indications for psychotherapy treatment performed during the reference period will be included.
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes all adult patients diagnosed in the reference period.
Exclusion criteria	Patients younger than 18 years and those not residing in the geographic area of study.
Indicator Type	Process
Data sources	Patient clinical history.

Indicator	Psychotherapy in mild-moderate depression
Justification	Some psychotherapeutic treatments have been shown to play a significant role in the treatment of depression. This indicator is to monitor the degree of coverage of psychotherapy in mild-moderate depression.
Formula	Number of adult patients with a recorded diagnosis of mild-moderate depression treated with psychotherapy ---------- x 100 Number of adult patients with recorded diagnosis of mild-moderate depression
Description of terms	Patients treated with psychotherapy: Those receiving any of the duly validated treatments. Brief psychotherapy: Psychotherapy not exceeding 6-8 sessions over 10-12 weeks. Adult patients: Patients over 18 years with recorded diagnosis of depression and start of indication of treatment with antidepressants during the reference period will be counted. Recorded diagnosis of depression: Written record of the diagnosis in the patient Medical History that a new diagnosis of mild depressive disorder was made in the reference period. New episodes in patients with a history of depressive disorder will also be counted. Patient Medical History: Information from Primary Care and/or hospital Clinical History on paper and/or electronic format. Indication of treatment: All new indications for psychotherapy treatment performed during the reference period will be included.
Geographical reference area	The geographic reference area for the population residing there who are diagnosed with major depressive disorder in the study period.
Reference period	Generally the last 12 months, but includes all adult patients diagnosed in the reference period.
Exclusion criteria	Patients younger than 18 years and those not residing in the geographic area of study.
Indicator Type	Process
Data sources	Patient clinical history.

12. Diffusion and implementation

The clinical practice guidelines are tools to promote greater quality and equity in the delivery of healthcare and to assist decision making. Its main purpose is to convert scientific knowledge into specific recommendations, so their diffusion, dissemination and implementation are crucial.

However, implementation strategies remain a challenge, despite the significant methodological improvement and increase in the production of clinical practice guidelines in recent decades in Spain. This challenge is common to most health systems, since there is a lot of evidence referring to the difficulties of implementing the recommendations and proposed algorithms.

Specifically in the field of mental health, adherence to CPGs in daily practice can still be considered low[390,391]. Thus, in Spain only 31.2% of patients with major depression receive adequate treatment according to the CPG, according to the *European Study of the Epidemiology of Mental Disorders* (ESEMED)[12].

12.1 Diffusion and dissemination

There are 2 versions of this CPG: the full and summary versions, as well as a document with information for patients and relatives and a document with methodological material. The full version, the information for patients and the methodological document can be accessed through the websites of the Galicia Health Technology Assessment Agency, avalia-t, (http://avalia-t.sergas.es) and GuíaSalud (http://portal.guiasalud.es).

The strategies outlined for the diffusion and dissemination of this CPG are:

- Official individual delivery of the guideline to potential professional users by the health authorities.
- Diffusion in electronic format on health service websites and those of companies and associations involved in the management of depression.
- Incorporation of the guideline to CPG compilation databases, both nationally and internationally.
- Distribution of information to patients and relatives by working with different patient groups.
- Presentation in primary and specialty care through interactive lectures and workshops with patients, family members and stakeholders.
- Presentation of the guideline in scientific activities (conferences, congresses and meetings).
- Online and/or workplace training on the evaluation and management of patients with depression.
- Publication of the guideline or studies derived from it in scientific journals.
- Establishing clinical decision support systems to integrate the guideline and selected indicators in the software used in primary care, emergency services and specialist care.
- Translation of the full version into English.

12.2 Implementation of the CPG through integration into the electronic medical record

One of the strategies proposed in the past decade to facilitate the implementation of guidelines is the development of systems to incorporate them into routine workflows[392]. For example, knowledge management (KM) and clinical decision support systems (CDSS) could have a crucial role. There is evidence that their implementation can lead to improvements for both patients and organisations, although the effectiveness of these systems is influenced by various aspects, such as the scientific knowledge available, contextual factors and their interaction with users[393].

KM systems are "tools that provide relevant information according to the characteristics or circumstances of the clinical situation, which require interpretation for direct application for a particular patient". Furthermore, CDSS may be defined as "any electronic system designed to support clinical decisions, which provide recommendations based on the features of the patients"[393].

One way to implement a clinical decision support system is via the electronic medical record (EMR). Different studies have shown increased adherence to CPG recommendations and improved health outcomes through their joint use by CDSS and EMRs[394-396.] Thus, the EMR could be a promising tool for improving the care provided to patients with depression, through proper documentation and provision of recommendations on handling or interacting with information that may be helpful in making decisions in clinical practice[397.] Furthermore, there is growing consensus on the need for the computerisation of guidelines and their integration with electronic medical records[398].

Key question

- What is the progress and impact of clinical decision support and knowledge management systems on the management of depression?

In 2012, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review of the evidence regarding the progress and impact of clinical decision support and knowledge management systems[393]. Although this did not specifically include studies on depression, it was selected to evaluate the evidence related to the progress and impact of these systems which may be common for any pathology and the depression studies will be specifically reviewed.

This review included 311 studies, of which 47.5% were RCTs (n = 148), 38.9% were of quasi-experimental design (n = 121) and 13.5% were observational (n = 42). No qualitative studies were included, although some RCTs had components that evaluated the satisfaction of both staff and patients. The resources most commonly incorporated into the CDSS were taken from protocols (61 studies) and CPGs (42 studies). Most studies focused on a specific guideline or pathology (107 studies, 72.3%) or a small number of conditions (41 studies, 27.7%). Many of the 42 studies computerising guidelines focused on cardiovascular diseases (n = 17) and only 3 of the RCTs specifically addressed the implementation of a mental health CPG, regarding depression in 2 cases.

The authors of a meta-analysis[393] confirmed 3 aspects previously described in the literature that influence the overall success of implementing CDSSs: SR 1+

- Automatic input of information as part of the workflow.
- Providing support at the time and place where decisions are made.
- Providing recommendations, not just assessments.
- And then added 6 new ones:
- Integration with the system input to ensure introduction into the workflow.
- No need for entering additional clinical data.
- Promotion of action rather than inaction.
- Evidence-based justification for a decision.
- Involvement of professionals in the development of the tool.
- Making it easier for staff and patients to make decisions.

Once the CDSS and/or KM systems were implemented and changes were made in the care process and the variables evaluated, the following was found[393]: SR 1+

- 29.1% of the studies included in the review assessed their impact on conducting preventive measures and found a significant improvement.
- 19.6% of the studies evaluated the impact on the conduct of clinical studies and found a significant increase in them.
- 45.3% of the studies analysed the impact on the prescription of recommended treatments and found a significant increase.

The work revealed a high clinical acceptability, with rates above 75%, and high satisfaction with integrated systems, although it is worth noting that few studies have examined these variables. SR 1+

No study evaluated the organisational changes associated with the adoption of these systems, nor the impact of patients seen/unit time or workload. Also, the evidence on efficiency was limited, although there appears to be a favourable trend towards the incorporation of these systems.

12.2.1 Benefits of Clinical Decision Support Systems in depression

The AHRQ report included 3 studies on the incorporation of CDSSs in the management of de

The first compared the effect of including 2 recommendations on screening and the diagnosis of depression in computerised format vs manual (using a checklist) in a mental health unit. The rate of identification and diagnosis according to DSM-IV significantly increased in the computerised version. It is worth noting that the CDSS and electronic medical records had to be used in parallel for this study[399]. RCT 1+

Another study conducted in primary care compared electronic *feedback* about the diagnosis (after the module identified a patient who may have had depression, the EMR issued an interactive alert which required an obligatory response) with the standard management of depression and using paper reminders. No differences between the groups were found in the rate of agreement or the treatments used in the 3 conditions tested. However, the professionals who agreed with the diagnosis (65% of 186 clinical ones) documented it to a greater extent and prescribed significantly more drug treatment and referred more patients to specialised care[400]. — RCT 1+

A small non-randomised trial that compared the effectiveness of the algorithm for depression in the *Texas Medication Algorithm Project* with standard therapy in primary care found that patients whose practitioners used the CDSS showed a significant reduction in depressive symptoms[401]. — Open label study 2+

The update to the AHRQ report included 2 studies on the use of integrated systems for the management of depression[402,403]:

These quasi-experimental design studies evaluated the effectiveness of CDSSs in screening for depression after a stroke[402] and in screening for bipolar disorder in patients diagnosed with depression[403]. The CDSS significantly improved the amount of patients who underwent screening and those who screened positive were more likely to have received proper treatment[402,403]. — 2+

Although there is positive evidence of the effect of the implementation of decision support systems in the management of depression, it is still necessary to investigate the issues that may affect their implementation in the EMR farther; as these can be influenced by the CDSS content, the recipients of the tool, the type of variables measured in the studies and the specific aspects of implementation[393]. In addition, the evidence has some limitations, among which are the variability in the type of tool, samples, areas and variables; and the absence of key implementation features, which are not considered or explicitly described in the RCTs reviewed. Future research in this field should aim to investigate issues such as content, technical features of the programs used and relevant variables to evaluate the real impact of their use in health systems.

12.2.2 Selection of content or recommendations to integrate into the information system

The CPG typically involves large clinical areas and so often contains a large number of very extensive recommendations. Therefore, the content must be organised and prioritised before it can be computerised. Also, it has been suggested that those areas and recommendations that could have a major impact on the improvement of care given and health outcomes of patients should be identified. Different criteria could be used to select these key recommendations and, although they may vary with the clinical process concerned, their priority was proposed with the below features[404]:

- Having a high impact on health outcomes and in reducing variability in clinical practice.
- Leading to more efficient use of resources.
- Promoting immediate health care and standardisation of the process.

Other authors have proposed that an excessive choice of content could lead to the tools being too one-dimensional. Thus, the need to integrate recommendations for diagnosis, treatment and follow-up, as much as is possible, could guide the clinician in most interventions[405].

In addition to the recommendations, integrating management algorithms could be key in implementing guidelines. The inclusion of algorithms with different treatment alternatives increases adherence to the guidelines, as it allows professionals to have greater flexibility in prescribing treatment or recommendations for patients with different factors or in different circumstances[406].

It would also be of interest to include information for patients so that staff could have information related to the pathology of interest. Patient information documents promote self-care, for making informed decisions and improving the effectiveness of care, and, although not sufficiently investigated, the actual impact of its use, there is evidence on satisfaction and perceived usefulness of this type of material in the field of mental health[407]. In fact, it has been considered an important factor in previous experiences of implementation of recommendations related to managing depression[403].

12.2.3 National and international experiences in implementing depression guidelines via CDSS

Texas Medication Algorithm Project

The *Texas Medication Algorithm Project* (TMAP) is designed to promote the use of pharmacological algorithms in combination with clinical support and information to patients in the management of schizophrenia, bipolar disorder and major depression. The results of its application in the treatment of depression in primary care showed health improvements in patients whose clinical treatment followed the algorithm proposed in that guideline in 2004[392]. As well as evidence derived from the STAR*D study, it showed adherence to algorithms in the management of depression and had a positive impact on clinical practice. These results and the repeated failures of guideline dissemination as the only strategy led to the development and evaluation of a decision support system to implement the recommendations of the TMAP.

The computerised version of the TMAP (compTMAP) was developed for use in primary and specialised care, and includes issues related to the prevention, diagnosis and support for decisions about treatment and advice about side effects and monitoring. Although the data published on its effectiveness are still insufficient, the compTMAP was associated with improvements in reducing depressive symptoms compared with standard treatment in a small trial. Also, in this study, personnel indicated that the tool was easy to use and that they preferred this option to the standard treatment[401].

Some of the barriers encountered in implementing the CDSS were the different program domain among staff, as well as the need for technical, administrative and support staff to promote autonomy and flexibility in clinical practice. It is also necessary to have feedback from staff for a sufficiently long period before implementation to consider any needs identified and to make the necessary changes[406].

The general feedback from patients about the experience was positive, although some criticism of these tools is that they can be depersonalising and have a negative impact on the relationship between staff and patients[406].

Computerisation of the Management of Major Depression CPG adaptation in the Catalan Health Institute

The Catalan Government (Generalitat de Catalunya) Department of Health has promoted the project to computerise the SNS Management of Major Depression in Adults CPG adaptation[123] for use in all Catalan Health Institute (Institut Català de la Salut, ICS) primary care centres, and to integrate it as part of the clinical station (eCAP). The Depression Guideline project (GPC-DEPc) was developed by a multidisciplinary team of clinical experts from the most directly involved

scientific organisations, pharmacologists, ICS general practitioners and computer experts.

The GPC-DEPc is a support system for clinical decision making fully integrated in the primary care Electronic Medical Records. There are 2 levels of support: a) Simple, using the common screen for pathological alert indicators for each patient, and b) a more specific one, using voluntary access to the support modules for clinical diagnosis, treatment and follow-up for patients with depression.

It is designed so that it can be used during the normal work flow and facilitate the recording of symptoms and access to consultations in each scenario at the same time during the patient visit. The clinician can accept or deny the recommendations proposed at any time, and record them automatically. These recommendations are based on logical algorithms for each module, integrating the updated process clinical information with relevant background information (e.g. age, sex, health problems and active prescription). The common integrated alert screen has automatic indicators for diagnostic suspicion, inadequate control, change of clinical status, future monitoring activities and access to recommendations for patients (printable pdf). The GPC-DEPc can be activated voluntarily if depression is suspected or after the proposed screening in special clinical situations (e.g. prescribing antidepressants without psychiatric diagnosis, or recent diagnosis with high comorbidity and depression). Screening is simple with only 2 questions. The depression module in the MINI-Interview provides diagnostic support. In cases where there is suicidal ideation, a suicide risk assessment is obligatory via the questions in the corresponding module in the same interview. SNS CPG therapeutic recommendations (e.g. psychotherapeutic, pharmacological or consultation with a specialist) are made from the clinical severity segmentation using the PHQ-9 and GAF scales. If the guideline detects intolerance or contraindications to the proposed drug treatment, an alternative treatment is offered, with a report on the reason for the contraindication or requirement for caution.

The difficulties in achieving meaningful use of other guidelines previously in the same eCAP computerised system may be partly due to the use of standard implementation methods. Therefore, a controlled study[408] was initiated to determine whether an implementation process with multifaceted strategies may be more effective. The assessment was conducted by analysing the degree of use and the key outcomes of the guideline itself, the maintenance of effects over time, both in patients and in staff and the cost-effectiveness analysis. This study may help identify strategies for more effective implementation.

Evidence summary

1+	Although there is positive evidence of the effect of implementing decision support systems in the management of depression, it is necessary to further investigate the issues that may affect its implementation in the EMR, which may be influenced by aspects such as the content included, the characteristics of the recipients of the tool, the type of variables measured for assessment and the specific implementation issues[393,399-403].

Recommendations

√	Recommendations on the management of depression in integrated systems in electronic medical records should be implemented.

13. Future research lines

Some aspects of the management and treatment of depression which have not been sufficiently studied have been identified while preparing this guideline. Future research should be done to provide more knowledge about these to improve the available evidence and reduce uncertainty in clinical practice; and therefore to contribute to the increased well-being and quality of life of patients with depression.

Perspectives of patients/relatives and health professionals:

- Perform qualitative studies to study the beliefs and experiences of patients with depression and their relatives, and their interaction with health systems.
- Investigate whether the qualitative evidence available in relation to the experience of depression can be extrapolated to Spain or whether there are specific cultural and social factors that could be key in managing this condition.
- Conduct research on the perspectives of health professionals regarding the management of depression in Spain to analyse the key factors for improving clinical practice.

Evaluation and screening for depression:

- Conduct studies to find out the clinical impact and barriers/facilitators for self-reporting and expert interview scales in the initial evaluation and monitoring of depression.
- Study the cost-effectiveness of screening programmes in risk groups at different levels of care.

Collaboration models and interventions between primary care and mental health:

- Investigate the effectiveness of care and interprofessional collaboration models on the prevention, diagnosis and treatment of people with depressive disorders.

Psychotherapy and psychosocial interventions:

- Investigate the efficacy of different types of psychotherapy at different care levels in the Spanish healthcare context.
- Assess the role of psychotherapy in preventing relapses, especially in patients with recurrent depression.
- Investigate aspects of delivery formats, professional training and psychotherapy structure that can influence efficacy in clinical practice, especially for cognitive-behavioural therapy and interpersonal therapy.
- Farther study the variables that can predict the efficacy of psychotherapy and the most appropriate intervention for particular subgroups.
- Investigate the active components in different psychotherapies and if varying these components can lead to different results.

– Validate and develop materials for self-help programmes and for computerised psychotherapy formats.

– Perform studies on the efficacy of low intensity psychotherapy, and whether computerised formats could be a viable option in the management of depression in the Spanish health system.

– Study more about the moderating variables of the efficacy of psychotherapy, especially those related to the therapist.

– Evaluate the effectiveness of psychological interventions for high and low intensity in dysthymic disorder and persistent subclincal depressive symptoms.

Pharmacotherapy:

– Include self-reporting and expert interview scales to assess depressive symptoms and incorporate variables related to the quality of life and functioning of patients.

– Conduct studies where variables such as the onset of clinical improvement and the optimal duration of pharmacological treatment in each risk group, drug and dose are analysed.

– Study more about the comparative efficacy of newer antidepressants in well-designed and long-lasting clinical trials.

– Investigate the efficacy and effectiveness of newer antidepressants in patient subgroups, such as those with different types of comorbidity or the elderly.

– Assess the acceptability of different antidepressant treatments and other moderating variables.

– Compare the side effects of different drugs in observational studies of larger sample size and methodological rigour, with special subgroups (such as in pregnancy and lactation).

– Evaluate the advantages of incorporating pharmacogenetics at the onset of clinical depression improvement and evolution.

– Evaluate the effectiveness of high and low intensity psychological interventions in dysthymia.

– Conduct studies to evaluate the efficacy of different antidepressants in dysthymic disorder and persistent subclinical depressive symptoms, compared with psychological interventions and placebo.

Resistant depression:

– Conduct studies to establish the efficacy of changing psychotherapy when the first antidepressant has failed and, vice-versa, the efficacy of changing to antidepressant treatment when psychotherapy has failed.

– Conduct studies to establish the optimal pharmacological strategy after failed responses to drug treatment: increasing dose, changing antidepressant, combining antidepressants or enhancement with other drugs.

- Conduct studies of comparative efficacy of different drugs in patients who do not maintain remission in the continuation and maintenance phases, as well as the role of other treatments such as psychotherapy, electroconvulsive therapy, vagus nerve stimulation and transcranial magnetic stimulation.
- Conduct studies to find out more about the interaction of pharmacological and psychotherapeutic treatments in relation to variables such as severity, intensity of symptoms, recurrence and relapse.
- Evaluate the effectiveness of ECT in preventing relapse in cases of chronic recurrent depression that do not respond to psychotherapy or pharmacological interventions.
- Conduct studies to categorise the beliefs, experiences and satisfaction of patients and their relatives with ECT.

Other treatments:

- Investigate the role of different variables related to the clinical efficacy of transcranial magnetic stimulation, such as stimulation parameters and application and/or duration of treatment.
- Perform randomised clinical trials on the efficacy and safety of vagus nerve stimulation as a treatment for depression.
- Make further clinical trials to evaluate the effectiveness of exercise as a single intervention or as an adjunct in the treatment of depression, differing by subgroups of different severity.

Implementation of the CPG via the Electronic Medical Record:

- Evaluate different systems to integrate recommendations for diagnosis and treatment of depression in the EMR.

Annexes

Annex 1. Criteria for severity/progress specifiers according to DSM-5

Criteria for severity/progress specifiers for major depressive disorder: Single and recurrent* episodes
Specify current severity: severity is based on the number of criterion symptoms, the severity of these symptoms and the degree of functional disability. – Mild: Few, if any, symptoms or only those required to meet the diagnostic criteria (5 or 6 symptoms), the intensity of the symptoms causes discomfort but is manageable and the symptoms result in minor impairment in social or occupational functioning. – Moderate: The number and severity of symptoms and/or functional impairment are among those specified for mild and severe. – Severe: The number of symptoms is substantially in excess of that required to make the diagnosis; the severity of the symptoms causes great discomfort, they are not manageable and they interfere significantly in social and occupational functioning.
With psychotic features: Delusions and/or hallucinations are present. – With mood-congruent psychotic features: The content of all delusions and hallucinations is consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment. – With mood-incongruent psychotic features: The content of the delusions or hallucinations does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment, or the content is a mixture of mood-congruent and incongruent themes.
Remission status: – Partial Remission: Symptoms of the immediately previous major depresive episode are present, but full criteria are not met, or there is a period lasting less than 2 months without any significant symptoms of a major depresive episode following the end of such an episode. – Full Remission: During the past 2 months, no significant signs or symptoms of the disturbance were present. – Unspecified.
When describing the diagnosis, the terms are listed in the following order: major depressive disorder, single or recurrent episode, specifiers of severity/psychotic/remission, then all of the following specifiers applicable to the current diagnosis: – With anxiety – With mixed features – With melancholic features – With atypical features – With catatonia – With peripartum onset – With seasonal pattern (recurrent episode only)

* An episode is considered to be recurrent when a minimum period of 2 months has passed between episodes, during which the criteria for a major depressive episode are not met.
Source: DSM-5

Annex 2. Validated Spanish versions of the HRSD, MADRS and PHQ-9 scales

Validated Spanish version of the HRSD[100]

Items	Operating Valuation
1. Depressed mood (sadness, depression, helplessness, worthlessness)	0. Absent 1. These feeling states indicated only on questioning 2. These feeling states spontaneously reported verbally 3. Communicates feeling states non-verbally, i.e. through facial expression, posture, voice, and tendency to weep 4. Patient reports these feeling states in spontaneous verbal and non-verbal communication
2. Feelings of guilt	0. Absent 1. Self-reproach, feelings of letting 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 were dead or has thoughts of possible death to self 3. Thoughts of suicide or threats 4. Attempts at suicide (any serious attempt rates 4)
4. Insomnia early	0. None 1. Occasional difficulty falling asleep, i.e. more than half an hour 2. Difficulty falling asleep every night
5. Insomnia middle	0. None 1. Feels restless and disturbed during the night 2. Wakes during the night; any getting out of bed rates 2 (except for justified purposes, e.g. voiding or taking or giving medication)
6. Insomnia late	0. None 1. Wakes in early hours of the morning but goes back to sleep 2. Unable to fall asleep again if getting out of bed
7. Work and activities	0. No difficulty 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 patient, or indirectly via listlessness, indecision and vacillation 3. Decrease in time spent on 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 at interview 2. Obvious retardation at interview 3. Interview difficult 4. Complete stupor
9. Agitation	0. None 1. Plays with hands, hair, etc. 2. Wrings hands, bites nails or lips, pulls at hair

10. Anxiety (psychological)	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
11. Anxiety (somatic)	0. Absent 1. Mild 2. Moderate 3. Severe 4. Incapacitating Concomitant physiological signs of anxiety such as: - Gastrointestinal: dry mouth, flatulence, diarrhoea, belching, cramps - Cardiovascular: palpitations, headaches - Respiratory: hyperventilation, sighing - Urinary frequency - Sweating
12. Gastrointestinal somatic symptoms	0. None 1. Loss of appetite, but eats without encouragement from others. Feeling of heaviness in the stomach 2. Difficulty eating without urging from others. Requests or requires laxatives or medication for intestinal gastrointestinal symptoms.
13. General somatic symptoms	0. None 1. Heaviness in limbs, back or head. Backache, headache, muscle aches. Loss of energy and fatigability 2. Any clear-cut symptom is rated 2
14. Genital symptoms	0. Absent 1. Mild 2. Severe 3. Incapacitating Symptoms such as - Loss of libido - Menstrual disorders
15. Hypochondriasis	0. None 1. Self-absorption (bodily) 2. Preoccupation with health 3. Frequent complaints, requests for help, etc. 4. Hypochondriacal delusions
16. Loss of weight (complete A or B)	A. According to patient (first evaluation) 0. No weight loss 1. Probably weight loss associated with present illness 2. Definite weight loss (according to patient) B. Weighed by psychiatrist (following evaluations) 0. Weight loss of less than 500g in a week 1. Weight loss of more than 500g in a week 2. Weight loss of more than 1kg in a week (on average)
17. Insight	0. Acknowledges being depressed and ill 1. Acknowledges illness but attributes it to eating badly, climate, overwork, virus, etc 2. Denies being ill

Cut-off points	No Depression	Mild	Moderate	Severe	Very Severe
	0-7	8-13	14-18	19-22	> 23

Validated Spanish version of the Montgomery-Asberg Depression Rating Scale (MADRS)[106]

The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient, all relevant clues as well as information from other sources should be used as a basis for the rating, in line with customary clinical practice.

Please put a cross in the appropriate box for each item.

Items	Operating Valuation
1. Apparent Sadness Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression and posture. Rate on 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 (by patient) Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.	0. Occasional sadness in keeping with the circumstances. 1. 2. Sad or low but brightens up without difficulty. 3. 4. Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances. 5. 6. Continuous or unvarying sadness, misery or despondency.
3. Inner Tension Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.	0. Placid. Only reflecting inner tension. 1. 2. Occasional feelings of edginess and ill-defined discomfort. 3. 4. Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty. 5. 6. Unrelenting dread or anguish. Overwhelming panic.
4. Reduced Sleep Representing the experience of 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, light or fitful sleep. 3. 4. Sleep reduced or broken by at least two hours. 5. 6. Less than two or three hours sleep

5. Reduced Appetite Representing the feeling of 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.
6. Concentration difficulties Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. 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 ability to read or hold a conversation. 5. 6. Unable to read or converse without great initiative.
7. Lassitude Representing difficulty in getting started or slowness in initiating and performing everyday activities	0. Hardly any difficulty 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 Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.	0. Normal interest in the surroundings and in other people. 1. 2. Reduced ability to enjoy usual interest. 3. 4. Loss of interest in surroundings. Loss of feelings for friends and acquaintances. 5. 6. The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.
9. Pessimistic thoughts Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.	0. No pessimistic thoughts. 1. 2. Fluctuating ideas of failure, self-reproach or self-depreciation. 3. 4. Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future. 5. 6. Delusions of ruin, remorse or unredeemable sin. Self- accusations which are absurd and unshakeable.
10. Suicidal thoughts Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.	0. Enjoys life or takes it as it comes. 1. 2. Weary of life. Only fleeting suicidal thoughts. 3. 4. Probably better off dead. Suicidal thoughts are common, and 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 preparations for suicide.

Cut-off points	No Depression	Mild	Moderate	Severe
	0-6	7-19	14-18	20-34

Patient Health Questionnaire (PHQ-9)[108] ©1999 Pfizer Inc.

Over the last 2 weeks, how often have you been bothered by any of the following problems?

		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed. Or the opposite: being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
Total score:					
10	If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?	Not difficult at all	.....		
		Somewhat difficult	.....		
		Very difficult	.....		
		Extremely difficult	.....		

Cut-off points	No Depression	Mild	Moderate	Severe
	< 10	10-14	15-19	20-27

Annex 3. Main antidepressant drugs: pack size and cost

Drug	DDD/mg	Pharmaceutical form	Dosage/ mg	Number of tablets	Price/	DDD Cost/	Monthly Cost/
Citalopram	20	Coated tablets	10	14	3.12	0.20	6.0
				28	3.12		
			20	14	3.12		
				28	5.14		
				56	10.28		
			30	28	7.71		
Escitalo-pram	10	Coated tablets	5	28	4.4	0.39	11.7
			10	28	11.55		
			15	28	17.5		
			20	28	23.37		
		Drops	20 mg/mL	15mL	26.16		
Fluoxetine	20	Hard capsules	20	14	3.12	0.14	4.2
				28	3.12		
				60	5.26		
		Dispersible tablets	20	14	3.12		
				28	3.12		
				60	5.26		
		Drops	20mg/5mL	70mL	3.12		
				14mL	3.12		
Fluvoxamine	100	Coated tablets	50	30	3.84	0.26	7.8
			100	30	7.68		
Paroxetine	20	Coated tablets	20	14	3.4	0,41	12,3
				28	13.96		
				56	27.92		
Sertraline	50	Coated tablets	50	30	5.85	0,20	6,0
			100	30	11.7		
Reboxetine	8	Tablets	4	20	12.8	1,24	37,2
				60	35.86		
Duloxetine	60	Hard capsules	30	28	30.99	1,99	59,7
			60	28	49.58		
Mirtazapine	30	Coated tablets	15	30	8.54	0,57	17,1
				60	17.08		
			30	30	17.08		
			45	30	25.62		
		Orodispersible tablets	15	30	8.54		
			30	30	17.08		
			45	30	25.62		
Venlafaxine	100	Tablets	37.5	60	10.18	0,45	13,5
			50	30	6.79		
			75	60	20.36		
		Extended release cap-sules	37.5	30	5.09		
			75	30	10.18		
			150	30	20.36		
			225	30	30.54		
Desvenla-faxine	50	Extended release tablets	50	28	23.17	0.75	22.5
			100	28	37.06		
Bupropion	300	Modified release tablets	150	30	27.08	1.63	48.9
			300	30	43.34		
Agomelatine	25	Coated tablets	25	28	60.1	2.15	64.5
Moclobe-mide	300	Coated tablets	150	30	5.18	0,35	10,5
				100	17.25		
			300	30	10.35		
				60	20.7		
Tranylcypro-mine	10	Enteric-coated tablets	10	25	1.87	0.07	2.24
Trazodone	300	Tablets	50	30	2.87	0,56	16,8
			100	30	5.74		
				60	10.54		

DDD: defined daily dose. The prices listed in this table were updated in January 2014.
Source: Ministry of Health, Social Services and Equality. Information on the products included in the SNS pharmaceutical services (dispensable through pharmacies). Available from: http://www.msc.es/profesionales/nomenclator.do

Annex 4. Depression: information for patients, family and friends

This information was compiled from the scientific literature available at the time of publication

Acknowledgements

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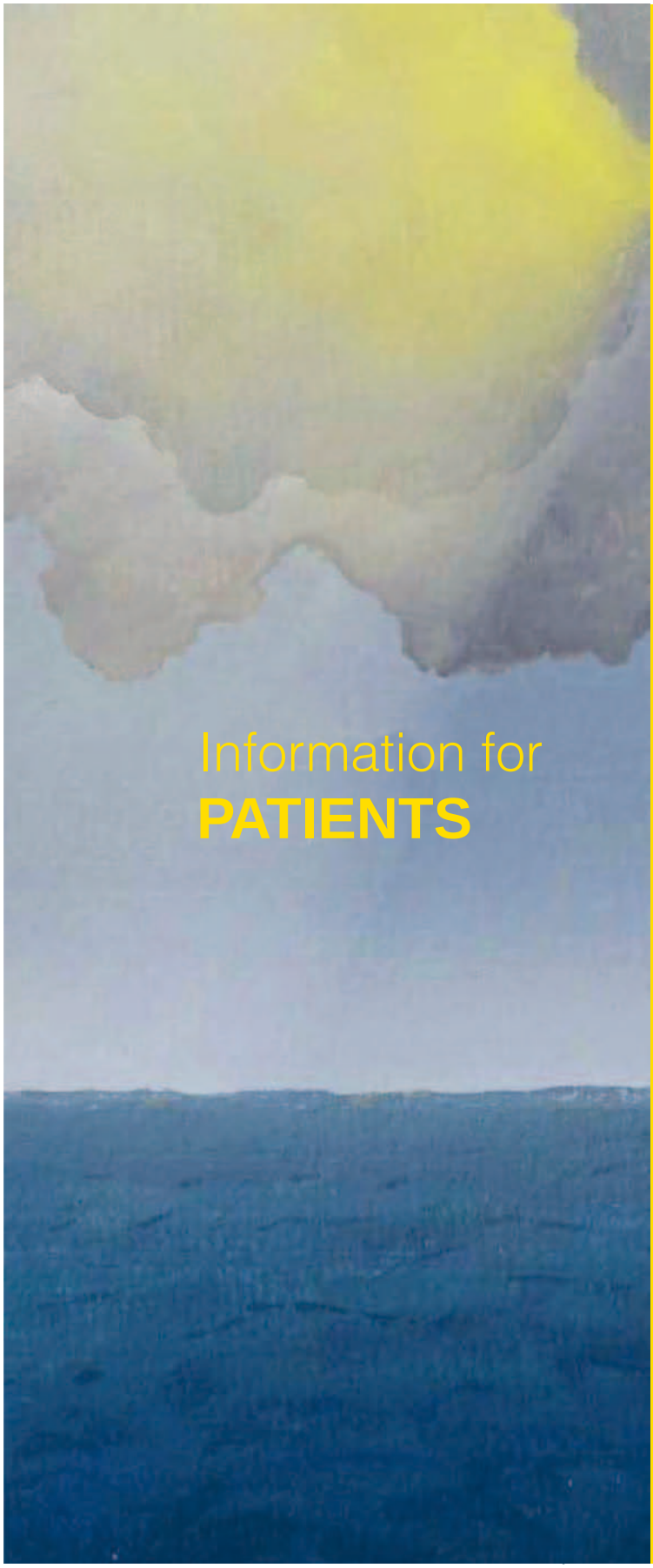


Some questions about depression

What is depression

Depression is much more than feeling sad.

Probably one of the most common mental disorders. The World Health Organisation (WHO) estimates that depression is a disorder that causes the most disability in the world.

In Spain, it affects 1 in 6 people at some time in their lives, and 70% of patients with depression are women. Depression can be suffered at any age.

Although most people experience sadness from time to time, usually in response to some event in their life (e.g. the loss of a loved one, unemployment or family problems), sometimes these feelings continue over time and are accompanied by other symptoms leading to distress and difficulty in leading a normal life. They can cause pain to both the sufferer and to those around them. This set of symptoms and feelings is what is known as **depression**.

Depression is a mood disorder characterised by **profound sadness and a continuing and** general **lack of interest** in things. It is also often associated with other psychological, physical and behavioural symptoms.

Depressed people often feel a certain helplessness about the situation and think they are weaker or less competent than others. This does not mean that depression has anything to do with self-worth or the ability to lead a normal life.

> The severity of depression can be very variable.

While some people do not seek help, most can improve their mood with the right treatment.

- In some cases, symptoms have little impact on daily life or do so only on some specific aspect: this is called **mild** depression.
- In other cases, many symptoms can occur which may eventually cause impairment or disability in different aspects of everyday life: this is called **severe** depression.
- Between mild and severe, there is **moderate** depression: when the symptoms and limitations are not so serious, not as specific nor as widespread as in severe.

> There is no reason to feel guilty or ashamed if you are depressed.

What are the symptoms of depression?

The symptoms of depression are very varied; it is not only feeling sad.

The frequency and intensity may vary from person to person, but the two most important are:

- **Low mood**, sadness and feelings of hopelessness.
- **Loss of interest** in activities that were previously enjoyable, or less pleasure taken from them for the majority of time over the previous weeks.

Other possible frequent **symptoms** are:

- Irritability (easily annoyed).
- Anxiety.
- Wanting to cry for no apparent
- reason.
- Loss of energy or tiredness. Sleep problems.
- Changes in appetite, which sometimes lead to an increase or decrease in weight.
- Difficulty concentrating or memory problems.
- Feelings of worthlessness or guilt.
- Negative thoughts, excessive self criticism.

Death wishes or thoughts of suicide.
The following associated physical **symptoms may also be felt:**

- Pain in different parts of the body, e.g. headaches.
- Palpitations or tightness in the chest.
- Abdominal discomfort or digestive problems.

If you have several of these symptoms most days, you should consider asking for help or consulting your family doctor.

Depression can make the smallest of tasks as difficult as climbing a mountain.

What causes depression?

The causes of depression are not known. What is certain and on which almost all professionals agree is that it happens not because you are doing something wrong or because you are weaker than others.

You may have missed something in your life that has triggered the depression, but usually the disorder is caused by a combination of **factors:**

- It seems unlikely to be due to a single cause: rather it may be the result of a combination of psychological, genetic and biochemical factors.
- Psychological or personality factors may also make you predisposed to depression.
- Various circumstances have been described that may lead to the feelings characteristic of depression and act as triggers.
- Some studies show that when people feel depressed it is reflected by changes in some areas of the brain. In addition, neurotransmitters, the chemicals that brain cells use to communicate, appear not to be in equilibrium.

Some of the **circumstances that may increase the risk of depression** are**:**

- Having suffered depression in the past. A history of depression in the family.
- Experiencing loss or stress, including the death of loved ones, unemployment, loneliness, changes in lifestyle or problems in interpersonal relationships.
- Conflict situations in the immediate environment (e.g. work, family or other contexts).
- Having suffered physical or psychological trauma.
- Serious physical illness or chronic health problems.
- Some drugs used for other conditions (check with your doctor).
- Alcohol or drug use.
- After giving birth: Some women may be more vulnerable to depression. The hormonal and physical changes along with new responsibilities with the newborn can be especially hard to take.

How is depression diagnosed?

The diagnosis of depression is normally performed by a GP, clinical psychologist or psychiatrist.

What is the evolution of depression?

The duration of depressive episodes is variable, but most people are well again after 4 - 6 months.

It is done via a clinical interview by considering the information provided by the patient, relatives and friends. Sometimes, questionnaires or tests are used to support the interview; usually to learn more about the type of symptoms or depression you may have.

The professional making the assessment will ask about your symptoms to find out the severity of your depression. Specifically, the following questions will be asked:

- Thoughts, feelings and behaviours.
- Duration of symptoms and how they affect your daily life.
- Level of daily activity.
- Relationship with family and friends.
- Any problems that may be related to the depression.
- Sicknesses in the past.

You should try to speak freely about things you consider of interest to understand what is happening to you. Interviews between patients and healthcare staff are regulated by laws that protect confidentiality.

It can sometimes be difficult to talk about your feelings; but remember that confidentiality and privacy are guaranteed.

To show **improvement, you should follow the treatment recommendations** from healthcare staff.

Some cases with symptoms lasting longer are referred to as chronic depression.

On the other hand, some people have depression only once in their life. However, the fact of having had depression may increase the risk of having it again.

If you are depressed, **remember**:

Depression is a treatable condition from which you can recover.

The fact of having depression does not mean you are weaker or less able to deal with things.

What can I do if I think I'm depressed?

Many people with depression do not get help or treatment because they do not think their symptoms signal an illness and can therefore not be treated.

If you think you may be depressed, ask for help.

Sometimes it can be difficult to ask for help because you may feel guilty about not being well, and you prefer to hide your problem.

You do not have to deal with depression alone. You can do any of the following:

- **Tell someone in your confidence**. For example, someone in your family, your partner, a friend or any other person with whom you feel comfortable: do not isolate yourself.
- **Talk to your family doctor or another healthcare professional.** This way, a proper diagnosis can be made, different treatment options offered and help given in making decisions about it.
- **If you have any thoughts related to death**, you should talk to someone in your confidence, who can be with you until you feel better. You can also call the emergency number (061) or request specific telephone support for patients with suicidal ideas (see section with additional information).
- **Contact a support group**. Some places have associations can offer this kind of help.

If you talk to someone and you feel they do not understand, try someone else.

Other possible recommendations are:

- **Learn** more about depression, so you can understand your symptoms and their significance better.
- **Try** exercising and eat healthily: it is advisable to start slowly, and you can ask friends and family to help you.
- **Avoid** exercise at the end of the day, close to bedtime.
- **Sleep** regularly: although some people with depression have insomnia, others sleep a lot. You should therefore follow a few rules to help you maintain sleep hygiene: such as going to bed at more or less the same time every day; not taking stimulants; and not falling asleep during the day. If these measures do not work, sometimes you will need to take a sleeping drug.
- **Avoid** alcohol and drugs: not only do they not help, but they will complicate matters further.

Do not think it's a matter of being strong or resorting to alcohol or drugs to solve your problems: these things do not help, and in fact make the situation worse.

What can the heath care system offer me if I'm depressed?

The health system can offer information, help and treatment

Information and support

Healthcare personnel can provide information about depression and therapeutic support. This is usually information about the causes and progression of the disorder, as well as treatment options and available resources.

If you do not understand something, it is better to ask rather than be in any doubt

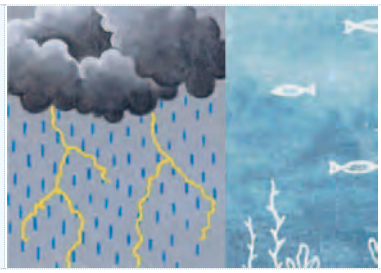
Health professionals

Your family doctor is probably the first person you can contact. Most people with depression can be efficiently attended to in primary care. As we have seen, because depression has different causes and seve ity, each person receives a personalised depression treatment.

Sometimes care from a mental health specialist is also required, especially if the depression does not respond to treatment or if you have had more than one episode.

How is depression treated?

The aim of treatment for depression is to make your symptoms improve, so you feel better and can get back to the way you were before



There are several proven treatments that can help. Sometimes you need to try more than one to find the right one, but this does not mean that they will not work.

The efficiency of any treatment depends largely on the cooperation between the patient and the people attending to you.

People with mild depression can improve on their own without treatment, or receive advice on how to address the problems or how to change some aspects of everyday life to help them feel better. Antidepressant drugs and psychological therapies are also useful in some cases.

Although some people use them, some alternative therapies are not recommended, such as acupuncture, yoga, massage, or certain food supplements.

St. John's Wort (a herbal therapy used by some people) has the disadvantage that it can seriously interact with some commonly used drugs, such as oral contraceptives, anticoagulants, anticonvulsants and some cancer treatments; so it is essential to use it with the same medical control as any other medicine.

For moderate depression, psychological therapies and antidepressants are the treatment options.

For severe depression, the recommended treatment is drugs combined with psychological therapy.

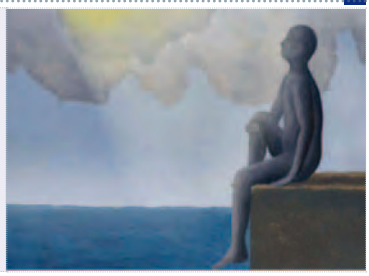
In some cases, when other methods have not worked and the symptoms are severe and disabling, electroconvulsive therapy (ECT) is indicated. Despite comments you may have heard, this is a quick and efficient treatment, administered in hospital under.

Note that there are health professionals skilled in the assessment and treatment of depression that can help you decide. The most appropriate treatment depends on the individual case and your preferences. The main thing is to find a treatment that works, and to give it the time needed to do so.

Keep in touch with your GP, especially if the treatment does not seem to help you improve. The expected results are not always produced by the first treatment proposed.

What can help?

The following recommendations are usually good for people with depression.



Some of these recommendations may not be effective for everyone. You should keep trying until you find the ones that make you feel better

Planning your day

When experiencing feelings of sadness or depression, it can be really difficult to keep going. However, maintaining a minimum of certain things to do helps you feel better.

- You can make a list of things you intend to do each day (with somebody's help if needed).
- At first, do not be too hard on yourself.
- You should as far as possible do things you like at least once a day.
- Do something physically exerting every day.
- If you do not complete some part of your plan, go on to the next activity.
- If you do not feel like doing anything at all, it may be helpful to do something with other people.
- See how your mood changes depending on your progress and share it with others.

Handling stress

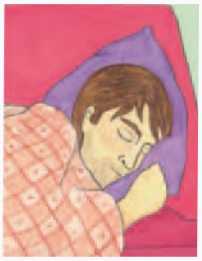
- If your problems seem overwhelming, take them one by one, if possible.
- Spend some time following your own interests.
- Learn to recognize when you need to stop; we all have a limit. Do not be too hard on yourself.

Physical exercise

- If you can, increase your physical activity gradually; and outdoors is better.
- A regular exercise routine is preferable, although any exercise is better than none.
- Group exercise can help you achieve your objective.
- If you are in any doubt about the most suitable exercise to take, check with your doctor.

What can help?

Sleep hygiene



- Stay in bed resting while you sleep. If you cannot sleep or get comfortable in bed, get up and go to another room (you can watch TV or read) until you feel like going back to bed.
- You can also listen to the radio in bed, putting it at a low volume so you have to make a little effort to hear it.
- You should go to bed around the same time every night.
- Do something fun and interesting before bedtime, such as reading or listening to music.
- Avoid taking a nap during the day if you think it prevents you from sleeping at night.
- Avoid or reduce the intake of stimulants (coffee, energy drinks, cola, tobacco or alcohol), especially at night.

Avoid alcohol and drugs

- Taking alcohol or other drugs are not good solutions if you feel depressed, and can contribute or lead to other problems.
- Ask for help from your friends, family or your GP if you want to cut down or give up.
- If you think it necessary, there are specialised health devices to help treat these problems.

Psychological therapies

The health system can offer psychological treatments specifically designed for people with depression, provided by people with specific training in them who are skilled in their use.

Research has shown they are effective in treating depression and may help reduce relapses. However, when starting a psychological therapy, you should remember that they do not usually take immediate effect, and you need to wait a while to see if they are effective.

Pharmacotherapy

The main drugs used to treat depression are called **antidepressants**. These drugs work by increasing the levels of certain chemicals called neurotransmitters in the brain to help improve your mood.

Ask for information about the different types of antidepressants available from the health professionals attending you. If you have previously taken this type of treatment, it is also important to report on what your experience has been, when making a decision on the best treatment option for you.

Antidepressants do not lead to addiction and, as time passes, you do not have to take progressively more medication to feel the same effects.

- **You should take the medication as prescribed.** The dosage for some drugs needs to be gradually increased during treatment and gradually decreased at the end. In all cases, sudden withdrawal of the drug can have unexpected or adverse effects.

Most treatments take time to get results.

Pharmacotherapy

The period of time for drug treatment varies from person to person.

- **Before taking antidepressants, the person** needs to be informed that the medication needs time to lead to an improvement and determine if the drug is of any use (usually a few weeks). Therefore, if you have decided to start taking medication, you need to keep taking it as agreed, even if at first you question its benefits.

- Your GP or psychiatrist will inform you of the side effects expected with your medication. Most are tolerable for most people. Although antidepressants do not lead to addiction, you may experience some adverse effects (dizziness, nausea, anxiety or headaches) when stopping taking them. They are usually mild and disappear within a week or two, but sometimes have a greater intensity, especially if the medication is stopped abruptly. They are generally tolerable and temporary.

- **Normally, it is recommended to take the medication for at least 6 months after an improvement at the same dose**. Then, your family doctor or psychiatrist may advise lowering the dose or stopping it completely depending on the improvement or unpleasant side effects you experience, or if you want to end the treatment. If your symptoms do not evolve as expected, another treatment option may be considered.

The person suffering depression often has a very changeable mood over a few days or throughout the same day. Therefore, you should use the better moments and days to make an effort, and perhaps isolate yourself on the bad days and not force yourself to do too much.

Remember: if you have been prescribed an antidepressant drug, your doctor will explain:

- The symptoms it acts upon. Approximately
- how long will it take before it has an effect.
- How long to take it and at what dosage.
- The possible side effects.

Electroconvulsive Therapy

If you need this treatment your doctor will explain how it works and its advantages and disadvantages.

Electroconvulsive therapy is the most efficient treatment in very severe major depression that does not respond to other treatment.

Currently, it is performed safely in a hospital, without any pain and in most cases with no serious side effects.

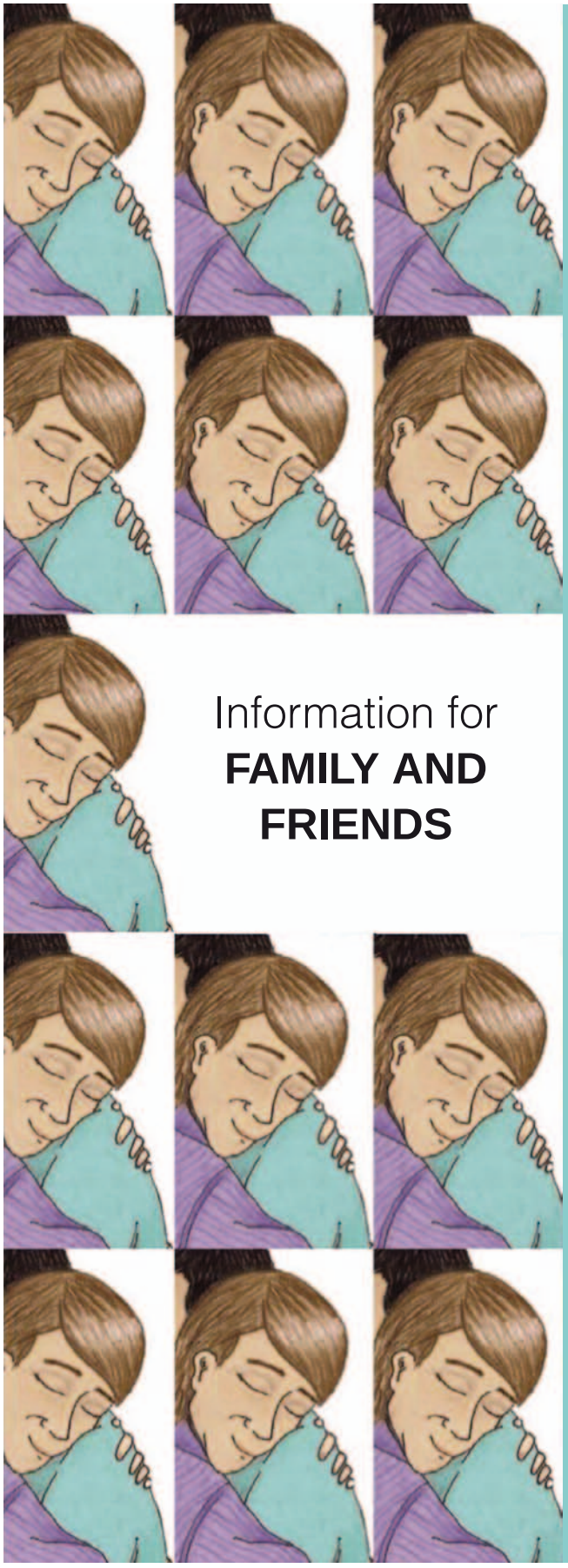
For more information

- **VISIT YOUR HEALTH CENTRE**
- **Emergency phone no: 061 or 112**
- **Spanish Confederation of Associations of Families and People with Mental Illness www.feafes.com**

(They provide information and support and have some psychosocial resources).

- **Telephone Helpline www.telefonodelaesperanza.org.**

(24-hour crisis telephone line in the main Spanish towns).



Information for
FAMILY AND FRIENDS

How I can help a family member or friend with depression?

How can I help a family member or friend with depression?

It can be very hard to see a loved one depressed. It would be very easy for you to feel overwhelmed or confused by what is happening

The family, partner and close friends of people wit depression have found the following **strategies us ful:**

Learn about depression, its treatment and what you can do to help your family member recover.

Do not force them to be more active; instead give them opportunities to share activities with you that they may be more willing to do.

Dedicate some of your time to be with him or her.

The person with depression wants to get better. If ever you think otherwise, it means you do not understand that this apparent lack of effort is just one of the symptoms of depression itself.

Criticism and reproaches activate feelings of depression; praise and encouragement increase self-esteem and cheer the person up.

Praise each step in their progress, no matter how small, and especially early on.

Help them to recognize the sources of stress and to find the most appropriate way to address them. Your help may be needed in solving some problems of particular concern to your loved one.

Lead a healthy life, do some exercise and have fun. Share these activities with your depressed loved one.

Help them to keep their commitments regarding the treatments agreed with medical staff.

Be an example and share restrictions regarding alcohol and other intoxicating substances with your loved one.

Take any thoughts of suicide seriously and show willingness to talk to him about this issue openly. If your loved one feels unsure about hurting himself, be there for him, tell him how much you need him and how valuable he is to you.

If you think you need assistance, you can contact medical personnel or use the emergency phone number (061). For this and wherever possible it is preferable to have the blessing of your loved one.

If you are caring for someone with severe depression you should also find time for yourself and to rest.

Do not feel bad or guilty for taking time out for yourself. When the depression drags on, living with your loved one can wear you out, so you need to take steps to look after yourself and stay well psychologically.

To take good care of your loved one, you need to take good care of yourself.

More information

- **VISIT YOUR HEALTH CENTRE**
- **Emergency phone no: 061 or 112**
- **Spanish Confederation of Associations of Families and People with Mental Illness www.feafes.com**

(They provide information and support and have some psychosocial resources).

- **Telephone Helpline**

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(24-hour crisis telephone line in the main Spanish towns).

Annex 5: Abbreviations

AD:	Antidepressant
AGREE:	Appraisal of Guidelines Research and Evaluation
AHRQ:	*Agency for Healthcare Research and Quality*
BDI:	*Beck Depression Inventory*
CBT:	Cognitive behavioural therapy
CES-D:	*Centre for Epidemiologic Studies Depression Rating Scale*
CPG:	*Clinical practice guideline*
DSM:	Diagnostic and Statistical Manual of Mental Disorders
ECT:	*Electroconvulsive therapy*
ESEMeD:	European Study of the Epidemiology of Mental Disorders
FDA:	*Food and Drug Administration (USA)*
FEAFES:	Federation of Associations of People with Mental Illness
HAM-D:	Hamilton Depression Scale
HRSD:	Hamilton Depression Scale
ICD:	International Classification of Diseases
IPT:	Interpersonal therapy
MADRS:	Montgomery-Asberg Depression Rating Scale
MAO:	Monoamine oxidase
NHS:	*National Health Service (UK)*
NICE:	*National Institute for Health and Care Excellence*
NNT:	*Number needed to treat*
PHQ-9:	*Patient Health Questionnaire*
QALY:	Quality-adjusted life year
RCT:	*Randomised clinical trial*
SADS:	*Schedule for Affective Disorders and Schizophrenia*
SIGN:	*Scottish Intercollegiate Guidelines Network*
SNS:	Spanish National Health Service
SSRI:	Selective serotonin reuptake inhibitor
TCA:	Tricyclic antidepressant
WHO:	World Health Organisation

Appendix 6: Glossary

Beck Depression Inventory (BDI): A self-administered, self-assessment scale primarily to assess clinical symptoms of melancholy and intrusive thoughts present in depression.

Befriending: Similar set of techniques to those used in supportive therapy.

Behavioural activation: A type of structured and brief treatment for depression based on learning theories, specifically in the observation that behaviour modification can have a positive effect on emotions.

Behavioural therapy: A clinical psychology approach based on the psychology of learning to explain psychological disorders and to develop strategies aimed at therapeutic change. Another feature is being based on the experimental study of the principles and laws of learning.

Bibliotherapy: A form of therapy in which written material is selected for the patient to read to treat emotional and behavioural problems. Professional intervention is minimal and reading texts leads to a process of self-help through the reflection of the patient.

Brief psychodynamic therapy: This is derived from psychoanalysis and is based on Freud's theory of psychological functioning that the nature of conflict may be largely unconscious; so the therapeutic goal is to resolve these conflicts.

Case-control study: Observational and analytical study in which subjects are selected based on having (cases) or not having (control) a particular disease, or in general a certain effect. Once selected, it is investigated if they are exposed to a feature of interest, and the proportion exposed in the case and control groups are compared.

Cluster B personality disorders: These include antisocial, borderline, histrionic and narcissistic disorders. As in other clusters, there is a degree of overlap between them, especially between antisocial and borderline personality disorders.

Cochrane Library Plus: Castilian Spanish version of the electronic journal, *The Cochrane Library,* which is the main vehicle for information from the Cochrane Collaboration. It is consulted via the Internet and updated every 3 months. It appeared in 2002 and is the only non-English version of the Cochrane Library.

Cognitive behavioural therapy: Focuses on changing dysfunctional behaviours, distorted negative thoughts associated with specific situations and maladaptive attitudes related with depression.

Cohort study: Following up of one or more cohorts of healthy individuals with different degrees of exposure to a risk factor, and in whom the onset of the disease or condition being studied is measured.

Comorbidity: A clinical situation in which the coexistence of two or more diseases or conditions occur, such as depression and anxiety.

Complete remission: The period of time in which the patient is asymptomatic, which is not a complete absence of symptoms. Examples of operational criteria used are less than 7 in the HRSD 17 scale, less than 8 in the BDI scale and a duration less than 6 months.

Contingency Management: Variety of operating techniques that share the common goal of controlling behaviour by manipulating its consequences.

Counselling: Advice or guidance in a psychological therapy that provides information and exchange of experiences based on 4 pillars: 1) assertive communication skills, 2) emotional support, 3) problem-solving model and 4) self-control.

Depression: Syndrome or group of symptoms in which affective symptoms (pathological sadness, lassitude, irritability, subjective feeling of distress and helplessness when faced with the demands of life) predominate. However, cognitive, volitional or somatic type symptoms are also present, in varying degrees; so one could speak of an overall impairment of psychic life, with particular emphasis in the area.

Dialectical behaviour therapy: Psychological treatment initially developed for the treatment of people with borderline personality disorder, but which is also used for patients with other diagnoses. It employs techniques that focus on behavioural change with validation or acceptance strategies, while stressing that acceptance does not preclude change (the dialectical component).

Effect of treatment: The impact of a treatment (intervention) on outcomes, i.e. attributable only to the effect of the intervention. Researchers try to estimate the true treatment effect using the difference between the results observed in the treatment group and the control group.

Effect size: This is a generic term referring to the estimate of the effect of a treatment when compared with the control group (for example, another active treatment, no treatment or standard treatment). An example of the effect size is the relative risk (used for dichotomous variables) and the difference in weighted and standardised means (both for continuous variables).

Effectiveness: The extent to which an intervention produces a beneficial result under ordinary circumstances.

Efficacy: The degree to which an intervention produces a beneficial result under ideal conditions. Randomised clinical trials are the gold standard in the assessment of efficacy.

Electroconvulsive therapy: A procedure consisting of provoking generalised seizure activity for therapeutic purposes, by electrical stimulation of the central nervous system.

***Embase (Excerpta Medica dataBASE)*:** A bibliographic database produced by the company Elsevier specialising in the field of biomedicine and pharmacology. It contains over 12 million records and has been consulted since 1974.

Expert interview scale: An assessment tool designed to be completed by an examiner, who must have different levels of professional training according to the instrument.

Family therapy: Making family relationships the main focus of the intervention, as some authors have suggested there is strong evidence of an association between child and adolescent depression and factors such as weak affective links, high levels of criticism, family hostility and parental psychopathology.

Guided Self-Help: An intervention using self-help materials, together with minimal guidance from a professional, to monitor progress, clarify procedures, answer general questions and provide general support or encouragement.

Hamilton Rating Scale for Depression (HAM-D or HRSD): Expert interview scale designed to measure the intensity or severity of depression. It is one of the most widely used in clinical practice and research to monitor the progression of symptoms.

Heterogeneity: This refers to the variability or differences in estimating the effect across studies in a meta-analysis. Sometimes a distinction is made between "statistical heterogeneity"

(differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in the key features of participants, interventions or outcome measures). Statistical tests of heterogeneity are used to assess whether the observed variability in the study results is greater than would be expected by chance.

Hopelessness: Cognitive schemas that share negative expectations about the future, be it the immediate future or more remote. The measurement of the Hopelessness construct was initiated by Beck and colleagues, with the development of the Beck Hopelessness Scale (BHS).

Interpersonal therapy: This deals with interpersonal relationships and intervenes in the immediate social context of the patient. It assumes that interpersonal problems can trigger or exacerbate depression; thus it focuses on them to promote adaptive changes leading to an improvement in depressive symptoms.

Locus of control: The degree to which a subject perceives his own behaviour is internal or external to the origin of events. An internal locus of control is the perception that events occur mainly as a result of one's actions, while an external locus of control is the perception that events occur as a result of chance, fate, luck or the power and decisions of others.

Medline: Bibliographic database produced by the National Library of Medicine in the USA. It includes references from articles published in over 4,500 medical journals since 1966. Each Medline record contains the basic bibliographic reference data for later retrieval. PubMed is an information retrieval system based on worldwide web technology for searching among databases, including Medline.

Mesh: Also called the *Medical Subject Heading*, is the controlled vocabulary used by Medline and other biomedical databases to process the information entered in each. It comprises over 33,000 terms arranged in hierarchical structures called trees, which are reviewed annually to ensure that they constitute an accurate reflection of current medical terminology and practice.

Meta-analysis: A statistical method combining the results of different studies to assess heterogeneity and provide overall results.

***Mindfulness*:** Also called full consciousness or attention, is the ability to pay attention to the experience as it is in the present moment, without judgment or evaluation.

Montgomery Asberg Depression Rating Scale (MADRS): Expert interview scale consisting of 10 items assessing the symptoms and severity of depression, obtained from the *Comprehensive Psychopathological Rating Scale.* It must be administered by a clinician although there are self-reporting versions.

NICE (National Institute for Health and Care Excellence): An independent British organisation that provides guidelines for health promotion and disease prevention and treatment in the *National Health Service.*

Non-directive therapy: A procedure in which the psychotherapist reflects what the patient says so as not to direct him or her. Its distinguishing feature is the attitude of the therapist, who promotes the therapeutic relationship to favour the processes of psychological change.

Observational study: A set of epidemiological studies where there is no intervention by the researcher, which it is limited to measuring the variables established in the study.

Partial remission: A period in which significant improvement is observed, but where the presence of more than minimal symptoms persist.

Peer support group: A group specifically created to help its members deal with a critical life situation, such as the chronically mentally ill, and secondly to inform, guide and support relatives by providing resources to withstand distress and cope with the prejudices related to lack of knowledge about certain diseases. These groups work independently and emerge in society when formal healthcare organisations do not meet certain requirements.

Problem-solving techniques: Training resources that facilitate coping with conflict and stress.

Problem-solving therapy: Psychological intervention aimed at increasing an individual's ability to solve problems focusing on coping with specific problem areas by the therapist and patient working together to identify, prioritise and manage these areas.

Psychoeducation: Individual or group format programmes that establish an explicit and instructional interaction between the practitioner, the patient and caregivers.

Psychosocial assessment: An evaluation consisting of different components, of which the most important are the assessment of psychological and social factors that may explain suicidal behaviour.

RAND/UCLA method: This is a consensus technique based on a modification of the Delphi method. This method makes it possible to combine the views of a number of experts to constitute a panel to discuss the use of a medical procedure.

Randomised clinical trial: An experimental study in which participants are randomly assigned over 2 or more options to receive a treatment or intervention. One group tends to receive conventional treatment (control group), which serves as a standard for comparison, while another group receives the treatment under study (experimental group).

Recovery: This is the duration of the remission period required to determine that complete recovery from the depressive episode has occurred. According to DSM-IV criteria, this period is 2 months.

Recurrence: Development of a depressive disorder in a person who has previously suffered from depression. A new depressive episode is usually considered to have occurred after 6 months.

Reinforcement: A positive reinforcement refers to the stimuli that increase the probability of emission of the behaviour that causes the appearance of such stimuli. When the behaviour increases as a result of the withdrawal of certain stimuli, it is said that the conduct eliminating those stimuli is negatively reinforced.

Relapse: Deterioration of an apparently controlled episode until it reaches a new diagnostic criteria level, occurring during remission and before recovery.

Remission: When the patient is asymptomatic, and is suffering nothing more than the minimum residual symptoms and total restoration of functioning has occurred.

Resistant Depression: A state partially responding, or not atall, to drug treatment, depending on the degree of intensity of the resistance, and therefore the strategy, for factors such as the response to treatment in previous and current episodes, the presence of risk factors and symptom profile and severity.

Response: No symptoms or a significant reduction in symptoms of depression for at least 2 weeks; or an improvement of at least 50% from baseline on a scale measuring depression.

Scheme: Within the framework of cognitive therapy, it is a structure for selective perception, coding and assessment of stimuli that affect the body and is used to structure and organise the medium in relevant psychic units.

Selective serotonin reuptake inhibitor: A class of antidepressant drug that inhibits serotonin reuptake by presynaptic neurons, and thereby increases the level of the neurotransmitter available for binding with the postsynaptic receptor.

Self-help: Learning or empowering codes of conduct or coping capacities for negative emotional states and situations without intervention or with minimal therapist involvement. It aims to give patients the knowledge and skills that facilitate overcoming or managing their health problems.

Self-reporting scale: An assessment tool designed to be completed by the individual.

Self-shaping: A technique that involves repeated viewing of a recording of the subject performing the desired behaviour aimed at achieving a goal.

SIGN (Scottish Intercollegiate Guidelines Network): An organisation formed in 1993 to develop and disseminate clinical practice guidelines with recommendations based on the best scientific evidence available.

Standard therapy: Care received by patients according to where this takes place. The definition of standard therapy or normal therapy varies with different studies, and includes different psychotherapeutic and/or pharmacological interventions.

Standard therapy: The normal treatment or care received by patients according to where this takes place and in the daily clinical setting. It is usually used as a comparison group in experimental studies.

Suicidal behaviour: Self-inflicted, potentially injurious behaviour in which there is evidence that: a) the person wishes to use the apparent intention of dying for some purpose, b) the person has some degree, determined or not, of suicidal intent.

Suicidal ideation: Thoughts (cognitions) about suicide.

Support groups: These are usually organised by a professional person and are composed of people who share some kind of problem that alters or modifies aspects of normal functioning. Sometimes these groups can be guided by trained professionals or supervised by paraprofessionals.

Support therapy: Based on emotional support, problem solving in a non-directive manner and reviewing the status of the patient (depressive symptoms, academic performance, suicidality, social activities), to assess the need for intervention by specialist professionals.

Systematic review: A form of research that provides a summary of existing research on a specific question, using systematic and explicit methods of identification, critical evaluation and synthesis of the literature.

Therapeutic alliance: Establishes an interpersonal relationship between the patient and the professional characterised by collaboration, consensus and results orientation. It is an essential component of the therapeutic process, since it favours communication, increased patient trust and collaboration over treatment.

Therapy including couples: A psychological intervention that aims to help participants understand the importance of interaction with others in the development and maintenance of symptoms, and therefore tries to change the nature of these interactions to obtain relationships based on support and a reduction in the level of conflict.

Treatment response: A reduction of 50% or more in a score based on standard depression scales. A reduction of between 25 and 49% of baseline values is a partial response, while a reduction of less than 25% is a non-response.

Waiting list: Term used in clinical trials to designate the group with which the experimental intervention is compared. It is characterised because the clinical variables of the participants assigned to this group are measured at the end of the waiting period, and they then receive treatment.

Appendix 7: Declaration of interest

Coordinators and members of the development group

María Álvarez Ariza, Gerardo Atienza Merino, María José Ávila González, Amparo González García, Guitián Delia Rodríguez, Elena de las Heras Liñero, Arturo Louro González, Jose Luis Rodríguez-Arias Palomo and Yolanda Triñanes Pego declared they had no conflicts of interest.

Expert contributors

Manuel Castro Bouzas, Ernesto Ferrer Gómez del Valle and Antonio Rial Boubeta declared no conflicts of interest.

Marlen Fernandez Silva declared receiving funding for continuing educational activities (several pharmaceutical companies) and as a speaker at conferences and courses (Boehringer, Janssen). Diego Palao Vidal declared receiving funding for continuing educational activities (Lilly), as a speaker at a conference (Servier), as an occasional consultant (Lundbeck), for medical research (Astra-Zeneca) and for continuous training at the Catalan Society of Psychiatry and Mental Health (several pharmaceutical companies).

External reviewers

José Angel Arbesu Prieto, Rosendo Bugarín Gonzalez, Carlos Calderón Gomez, María Consuelo Carballal Balsa, Francisco José Estupiñá Puig, Aurora Gavino Lázaro, Marta González Pescador, Raquel León Lamela, Cristina Losada Pérez, Antonio Madueño Caro, Manuel Portela Romero, Javier Sardiña Agra, Carmen Senra Rivera, Mikel Urretavizcaya Sarachaga and Fernando Lino González Vázquez declared no conflicts of interest.

Enric Aragonés Benaiges declared receiving funding for continuing educational activities (Esteve, Lilly) and for his role as a member of the advisory board of a research project (Lilly). Juan Luis Fernández Hierro declared receiving funding for continuing education activities (Pfizer) and as a speaker at conferences (Janssen-Cilag, Esteve). Guillermo Lahera Forteza declared receiving funding for continuing educational activities (Janssen, Lilly, Lundbeck) and as a speaker at a conference (Janssen, Lundbeck). Germán López Cortacáns declared receiving funding for educational programmes (WTO, Lilly). José Manuel Olivares Díez declared receiving funding for continuing educational activities (several pharmaceutical companies), as a speaker at conferences and courses (different pharmaceutical companies), for participation in clinical trials (different pharmaceutical companies) and as a consultant for different pharmaceutical companies. Antonio Olives Alonso declared receiving funding for continuing education activities (Spanish Federation of Family Therapy Associations). Manuel Serrano Vasquez declared receiving funding for continuing education activities (Astra-Zeneca, Otsuka, Janssen) and as a speaker at conferences and courses (FEGAS, Astra-Zeneca, Otsuka, GSK, Janssen, Lundbeck, Pfizer). Mercé Teixido Casas declared receiving funding as a speaker at a course (Lundbeck).

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