

5. Pharmacological treatment

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

5.1 Overall efficacy

A systematic review of 35 randomised clinical trials (RCTs) (with 2013 patients and several degrees of depression), in which low doses of tricyclic antidepressants (TCAs) (75-100 mg) were compared

with a placebo, showed that low doses of these drugs were 1.65 and 1.47 times more likely than the placebo to achieve a response at four and at six-eight weeks, respectively. The standard dose of TCA did not yield a greater response, yet there was an increase in the number of dropouts due to secondary effects⁶⁵.

Another subsequent systematic review (9 RCTs, 751 patients with a initial diagnosis of a depressive episode) assessing the effectiveness of TCAs versus “active placebos” found a statistically significant difference in favour of the active drug, although the analysis of the results showed a small slight, combined estimate of the effect in favour of the antidepressant, and there was heterogeneity in the outcomes due to a highly positive trial⁶⁶.

A meta-analysis of patients attended in primary care (15 RCTs of low quality, without reflecting the severity of the depression and using TCA in ten trials and SSRI in the rest or an association of the latter with TCA), demonstrated that drugs were more effective than placebo⁶⁷.

The NICE guideline does not recommend the use of drugs in mild depression because of their low risk-benefit ratio. It recommends considering them after the failure of other therapeutic strategies if there are associated psychological or medical problems or there is a prior history of moderate or severe depression²¹.

A large number of studies show efficacy in the response to placebo in moderate depression²¹, although there are authors who postulate the existence of over-estimation of the effect due to population skewing⁶⁸. Greater response and remission rates have been observed in the use of escitalopram and citalopram at high doses (20 mg and 40 mg, respectively) in 3 RCTs with a total of 1321 patients over 8 weeks⁶⁹⁻⁷¹. Likewise, a meta-analysis that included 6 RCTs with 1978 patients with a score of 15 on the *Hamilton Rating Scale for Depression* (HAM-D) demonstrated the efficacy of duloxetine versus placebo⁷². The remission rates were higher than placebo only with higher doses than those currently recommended for this drug ($p = 0.02$). Paroxetine, as an active comparator, also showed clinical efficacy and remission rates that were higher than placebo. In the treatment of moderate major depression, reboxetine was superior to the placebo in 5 of 12 short- and long-duration controlled studies and comparable in efficacy to active comparators in 3 out of 3 controlled studies⁷³. There are studies with prolonged release formulations, as in the case of

venlafaxine, which also showed statistically significant response and remission rates in comparison with placebo⁷⁴.

For severe depression, NICE includes solid data with respect to the SSRI response rate versus placebo, although the data are weak with respect to remission rates²¹. For reboxetine, the response rates in both hospitalised patients and in outpatients were higher than placebo (between 20 and 52%), as were its active comparators (desipramine, fluoxetine, imipramine). It also demonstrated significant differences in the remission rate⁷⁶.

Summary of the evidence

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

Recommendations

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

5.2 Comparative efficacy of drugs

The use of drugs for depressive disorders was generalised starting in the 50s after the discovery of imipramine and amitriptyline, the first ones to be effective. Amitriptyline inhibits the reuptake of serotonin and noradrenaline, thereby increasing their synaptic concentration, and it continues to be a standard drug in comparison studies of TCAs with other drugs. SSRIs appeared later, among which fluoxetine was the first that was shown to be effective, and it is the most used up to now⁷⁷. SSRIs are a heterogeneous class of drugs that cause the selective inhibition of serotonin reuptake, with a different strength than existing compounds. There are also differences in the secondary pharmacological actions, such as blocking the reuptake of noradrenaline and dopamine, the agonist action of the serotonin 2C receptors, the antagonist action of the cholinergic muscarinic receptors, etc. In recent years, a number of antidepressants, that act on adrenergic and serotonergic

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

Despite this therapeutic arsenal, around 38% of patients do not respond to treatment with SSRIs and new antidepressants during 6-12 weeks, and 54% do not reach remission⁷⁸.

TCA versus SSRI

The NICE²¹ depression guideline includes most of the studies published about TCAs, with sufficient samples to determine its efficacy in comparison with other types of antidepressants, its tolerability and its adverse effects. The comparisons included by NICE were amitriptyline with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine, imipramine, lofepramine, minaprine, nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine.

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

In a subsequent Cochrane review, neither statistically significant nor clinically relevant differences at decreasing symptoms were found in the response rates between fluoxetine and TCAs, or between the former and antidepressants in individual comparisons⁷⁷.

Table 5. Main antidepressants available in Spain.

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

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

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

Acceptability and tolerance of treatment

Fluoxetine had fewer early dropouts due to secondary effects than amitriptyline and other TCAs²¹.

Comparison between SSRIs

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

and the NNT for gaining an additional responder at 6-12 weeks was 14. No statistically significant differences were found in improvement of the symptomatology or in the response rates between fluoxetine and paroxetine, or between paroxetine and sertraline⁷⁸. These findings concur with a previous Cochrane review⁷⁷ in which statistically significant differences were found in efficacy and tolerability between fluoxetine and other antidepressants, although with an uncertain clinical significance and without being able to draw definitive conclusions for clinical practice.

Acceptability and tolerance of treatment

Efficacy studies do not indicate any substantial difference between SSRIs and new antidepressants regarding adherence to treatment. The most frequent and common side effects are the following: constipation, diarrhoea, vertigo, headaches, insomnia, nausea and drowsiness. Nausea and vomiting were the most frequent reasons for dropping out in efficacy studies⁷⁸.

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

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

Sweating was more frequent in patients treated with fluoxetine than in those treated with paroxetine, and nausea was more frequent in patients treated with fluoxetine than in those treated with fluvoxamine. As a class, SSRIs caused less weight loss than fluoxetine⁷⁷. Paroxetine caused more weight gains than fluoxetine and sertraline⁷⁸.

In most of the studies, sertraline showed an incidence of diarrhoea around 8% higher than the drugs with which it was compared (citalopram, fluoxetine, fluvoxamine, nefazodone and paroxetine), including second-generation drugs of other groups. Nevertheless, it is not clear that these findings can be extrapolated to other second-generation antidepressants⁷⁸.

Discontinuation syndromes (i.e. headache, vertigo, nausea) occurred in 0 to 86% of patients (referring to all second-generation drugs). Within SSRIs, the patients treated with paroxetine showed the highest incidence of this problem, while fluoxetine had the lowest incidence⁷⁸.

In head-to-head trials, paroxetine showed higher indices of sexual dysfunction than fluoxetine, fluvoxamine and sertraline⁷⁸.

There is scarce information about the comparative risk of rare but serious adverse events such as suicide, convulsions, hyponatraemia, hepatotoxicity and serotonin syndrome, which prevents solid conclusions from being proposed, although clinicians must keep in mind that these risks exist during the course of any treatment with a second-generation antidepressant⁷⁸.

Comparison between SSRIs/new antidepressants

A Cochrane review⁷⁷ did not find any statistically significant difference between fluoxetine and any heterocyclic antidepressant using a continuous outcome measurement. However, there are some studies that compared fluoxetine with bupropion, mirtazapine and trazodone; sertraline with venlafaxine and mirtazapine; paroxetine with duloxetine and venlafaxine; and citalopram with mirtazapine; and even though statistically significant differences were found in some comparisons, they were not clinically relevant.

The patients treated with venlafaxine had an additional effect (statistically not significant) of a 1.31-point reduction in the HAM-D 17 scale compared to those treated with fluoxetine. The NNT to gain one additional responder in 6 to 12 weeks with venlafaxine was 12⁷⁸. This analysis agreed with another prior study in which venlafaxine was statistically more effective than fluoxetine, both in a dichotomous and continuous outcome⁷⁷. However, venlafaxine has higher drop-out rates, it requires monitoring of the blood pressure, it shows a higher cardiovascular risk, and an overdose is more dangerous²¹.

The efficacy of reboxetine is similar to that of paroxetine⁷⁹ and citalopram (except in specific groups), and it has fewer problems of sexual dysfunction than both⁷⁹⁻⁸¹, although with more dropouts than citalopram due to adverse effects^{80, 81}.

Even though it is generally believed that the onset of the effect of antidepressant drugs does not occur until after 4 to 6 weeks have elapsed, there are hardly any studies designed with this variable as a measure of outcome, and some even contradict this belief. Thus, one meta-analysis observed that more than half of the patients who respond at 8 weeks begin to improve at the second week, and 75% in the fourth. Moreover, the lack of a response at 4-6 weeks is associated with a 73-88% likelihood that they will not start to respond in the eighth week⁸². Another review⁸³ observed that the therapeutic response to SSRIs is greater in the first week, with a progressive decrease in the following weeks, and a third study⁸⁴ observed that between 60% and 62% of the improvement takes place within the first 2 weeks of treatment.

Seven low-quality studies with a possibility of skewing found that mirtazapine has a faster onset of action than citalopram, fluoxetine, paroxetine and sertraline. The NNT to get one additional responder after 1 or 2 weeks of treatment was 7, yet after 4 weeks of treatment, most of the response rates were similar. Patients treated with escitalopram reached remission 7 days before those treated with venlafaxine. Likewise, those treated with citalopram showed a faster onset of effect than with fluoxetine, and there were no differences between them in the percentage of responders⁷⁸.

Acceptability and tolerance of treatment

When considering the total number of patients who dropped out during the trials, no statistically significant differences were found between fluoxetine and the various heterocyclic antidepressants⁷⁷. Patients treated with fluoxetine or sertraline had greater sexual dysfunction than those who took bupropion⁷⁸, while reboxetine had a high rate of dropouts, although it interfered less with sexual function.

Mirtazapine caused a considerably greater weight increase than other drugs (between 0.8 and 3 kilos after 6-8 weeks of treatment) and a greater number of patients who dropped out due to adverse reactions. Citalopram and escitalopram caused more nausea, tremor and flatulence than mirtazapine⁷⁸. In turn, paroxetine caused greater weight gains than fluoxetine and sertraline⁷⁸. On the other hand, an important observational study revealed that patients treated with venlafaxine showed a greater risk of suicide than those treated with citalopram, fluoxetine and dothiepin⁸⁵.

Suicide is an infrequent event, and clinical trials tend to be short-duration and have a small sample size, wherefore they don't have sufficient statistical strength to detect differences^{85, 86}. Meta-analyses, apart from including short-duration studies, do not tend to include suicide or the presence of any self-inflicted injury as a measure of outcome. There also are no meta-analyses that demonstrate a greater frequency of ideas, attempts or completed suicides in adult patients treated with antidepressants, although it is demonstrated in patients under 24 years of age⁸⁶⁻⁸⁸. The low frequency of this event and the fact that depression itself can have the same outcome as the treatment are the greatest

problems when interpreting the outcomes related to this subject, which means that the subject is not closed⁸⁶.

Comparison of new drugs between each other

There are few studies (some with insufficient statistical strength) for detecting significant or clinically relevant differences, wherefore the outcomes are not conclusive. In general, the differences found were of a modest magnitude, and their clinical implications are still undefined. Thus, the AHRQ⁷⁸ review found comparative studies between mirtazapine and trazodone without statistically significant differences regarding efficacy, and between venlafaxine and trazodone, with some results favourable to venlafaxine and a different profile of adverse effects: better sleep and more dizziness with trazodone and more nausea with venlafaxine.

After this review, a comparative study between mirtazapine and venlafaxine (with extended release) was published, which pointed out an early response with mirtazapine, independent from its sedative effect⁸⁹. Another study between trazodone (extended release) and sertraline was published, which did not show differences in the main outcomes, but it did show some in the adverse effects, such as a greater tendency towards sleepiness with trazodone and gastrointestinal disorders with sertraline⁹⁰.

No trials comparing directly duloxetine with venlafaxine were found, except one meta-analysis in which the efficacy and safety of extended-release venlafaxine and duloxetine were compared indirectly, without finding significant differences⁷⁴.

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

Summary of the evidence

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

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

Recommendations

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

5.3 Duration of treatment

The risk of recurrence in major depression is high. Thus, half of all patients have a new episode after suffering the first one, 70% after suffering two and up to 90% after suffering three⁹¹. Therefore, an important question when treating major depression is the time that the drug treatment must be maintained after recovery in order to prevent recurrence.

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

In general, patients who leave antidepressive treatment have a greater risk of recurrence than those who continue to take antidepressants, and theoretically, the patients with a greater risk of recurrence would be those who would benefit the most from an extended programme⁹³. Moreover, the more extended the treatment, the less difference there is between treated patients and controls in the risk of recurrence. In other words, the benefit of extending treatment decreases over time^{94, 95}. The goal of this question is to adjust the time of duration of the treatment after recovery to the type of patient.

In one double-blind study, 395 patients whose symptoms had previously remitted after 12-14 weeks of treatment with fluoxetine were assigned to one of the following options: 50 weeks of placebo; 14 weeks of fluoxetine, followed by 36 weeks of placebo; 38 weeks of fluoxetine, followed by 12 weeks of placebo, or 50 weeks of fluoxetine. The conclusion was that the treatment must be maintained a minimum of 26 weeks after recovery, given that the percentage of relapses was significantly greater in the patients with placebo treatment at 14 and 38 weeks. These differences between placebo and fluoxetine were smaller as the weeks elapsed, until there were no statistically significant differences at 62 weeks⁹⁴. In another double-blind study, these differences were statistically significant in favour of maintaining drug treatment for 12 months⁹⁶.

The information derived from a joint analysis of short-term studies (6-12 months) found a lower NNT in those treated for 12 months than in those treated for 6, which seems to advise maintaining treatment for one year after a first episode⁹².

The variable that is associated with a greater risk of recurrence and a greater benefit from maintaining treatment is the number of previous episodes^{99, 100}, and neither the response pattern⁹⁷ nor the recovery time after the start of treatment seem to have any relevance.

Finally, NICE recommends maintaining treatment with antidepressive drugs for at least 6 months after remission of the episode, at which time the patient is assessed for the possibility of extending treatment, thereby taking into account the number of previous episodes and the presence of residual symptoms²¹.

Summary of the evidence

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

Recommendations

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

5.4 Pharmacological strategies in resistant depression

There is no general agreement about when a depression should be considered resistant. In the consensus of the Fundación Española de Psiquiatría y Salud Mental [*Spanish Foundation of Psychiatry and Mental Health*], resistant depression is discussed when a patient does not improve after treatment using a drug with verified antidepressive action at therapeutic doses and during an adequate time⁹⁸. NICE defines it as depression in which the symptoms remain after two or more trials with antidepressants, and it considers those patients who do not respond to a single treatment trial as non-responders in acute treatment²¹. Following more restrictive criteria, other authors define resistant depression as the failure to reach remission after a suitable treatment trial with three different classes of antidepressants in suitable doses and time^{91, 93}.

In the STAR*D¹⁰⁰ report, after an initial, suitable treatment with citalopram, only 27.5% reached remission. Subsequently and successively, three more treatments were given in the event of intolerance or therapeutic failure, thereby obtaining an accumulated remission rate of 67%^{99, 100}. This seems to indicate that response rates decrease to the extent that more therapeutic trials are performed, wherefore there is a degree of resistance. Moreover, after four successive attempts of treatment, up to 32% of patients had not satisfactorily improved.

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

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

Dose increase

In a systematic review¹⁰¹ that included studies that analysed the increase of antidepressants in patients with resistant depression, among other strategies, the following results were obtained:

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

- ~ In 4 studies that analysed the efficacy of a dose increase of different SSRIs (fluoxetine, paroxetine, sertraline) in patients who were non-responders to a first trial of 3 weeks of treatment with SSRI at medium doses, it was observed that a dose increase did not significantly improve the results versus maintaining the dose and that dose increase caused a rise in the dropout rate due to adverse effects. However, there are data that point to the fact that in patients with severe depression, it is necessary to begin with high doses as from the start of treatment.
- ~ In another study with non-responder patients after 6 weeks of treatment with sertraline at a dose of 100 mg/day, the response rate after 5 more weeks of treatment was lower when the dose was increased to 200 mg than when the initial dose was maintained or it was augmented with 30 mg of mianserin.
- ~ The only heterocyclic antidepressant studied in resistant depression was maprotiline, and unfavourable data were obtained.

Antidepressant switch

A comparative study of sertraline versus imipramine in patients with resistant depression did not obtain sufficient evidence to determine if a switch between both drugs favoured a response by reducing the depressive symptoms, although the switch to sertraline reduced the risk of early dropout¹⁰².

Likewise, another study compared venlafaxine to paroxetine, and it obtained a significant difference in favour of venlafaxine regarding the likelihood of reaching remission¹⁰³.

Regarding the use of monoamine oxidase inhibitors (MAOIs), there are no data on using them in resistant depression due to a lack of randomised studies. There are only indications of a response in patients who have resistant depression with atypical symptoms and in major depressions and melancholia¹⁰⁴.

After not obtaining a therapeutic response with citalopram, no significant differences were observed with three treatment alternatives: venlafaxine, sertraline and bupropion¹⁰⁰. Another study also did not show that nortriptyline or mirtazapine improved remission rates after two failed treatments, the first with citalopram and the second with an increase of the dose or adding bupropion¹⁰⁵.

Finally, one study compared tranylcypromine with the association of venlafaxine and mirtazapine after the failure of three different treatments, without observing differences in the remission rates, although it did observe differences in the dropout rates due to tolerance, which were less with the combination of venlafaxine and mirtazapine¹⁰⁶.

Combinations of antidepressants

The systematic review prepared by NICE included several studies that compared the outcomes of patients who took two antidepressants versus a single-therapy at a standard dose or high doses²¹. The combinations were the following:

- a) SSRI plus mianserin vs. SSRI.
- b) several antidepressants plus mirtazapine vs. several antidepressants.
- c) amitriptyline plus moclobemide vs. amitriptyline.
- d) sertraline plus mianserin vs. high doses of sertraline.
- a) fluoxetine plus desipramine vs. high doses of fluoxetine.

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

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

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

Augmentors

NICE²¹ includes ten studies that compared an antidepressant plus lithium vs. an antidepressant plus placebo, and the antidepressants included were clomipramine, desipramine, imipramine, nortriptyline and citalopram. The results found significant differences in the response rates in favour of augmentation with lithium, and no data were found to indicate that the remission rates improved. Even though augmentation with lithium seems to be less tolerated by patients, there is insufficient evidence to determine if it is due to adverse effects.

Regarding the use of anti-epileptic drugs as augmentors in resistant depression, the data existing in literature are insufficient. Thus, there are no controlled studies with carbamazepine, although there are some observational studies, and numerous adverse effects are found. There are no positive data with lamotrigine, the data are insufficient with valproate, and there are no data with other drugs of this group, such as gabapentin or topiramate²¹.

Augmentation with pindolol was analysed in 6 studies in which an antidepressant plus pindolol was compared to an antidepressant plus placebo²¹. The authors conclude that even though there are data indicating that remission is favoured by adding pindolol, the effect is not evident in terms of response or in the average score of the scales. No effects were observed in the initial assessments of patients with resistant depression, and there are no long-term assessment data. The data were insufficient with respect to tolerability, and there are no clear data about the optimum dose and the duration of treatment.

One study in which desipramine or imipramine plus triiodothyronine or placebo was used observed significant differences in the response rates, even though the information was insufficient with respect to the reduction of the depressive symptoms¹⁰⁸. Due to its adverse effects, triiodothyronine must be used with caution in patients with a cardiovascular pathology, and care must be taken when associating it with tricyclic antidepressants²¹. The results of antidepressant augmentation with triiodothyronine or lithium showed similar results in the remission rates, although the dropouts due to intolerance were higher with lithium¹⁰⁹.

Five studies analysed the augmentation of antidepressants with benzodiazepines (BZDs) or with placebo, but the data were insufficient for determining if they have any augmenting effect in terms of efficacy and tolerability²¹.

One study compared the augmentation of fluoxetine plus buspirone versus placebo. No augmenting effect by buspirone was observed, and the data regarding differences in tolerability were insufficient¹¹⁰. Another study comparing methylphenidate associated with

various antidepressants, did not detect significant differences with respect to placebo¹¹¹. Finally, augmentation with buspirone versus augmentation with bupropion¹¹² in patients who did not remit with citalopram did not show differences with respect to remission rates, although there were significant and relevant differences regarding dropouts due to secondary effects.

Regarding the use of atypical antipsychotics, NICE only found one study that compared fluoxetine plus olanzapine or placebo²¹ showing significant differences in the response rate, although with insufficient evidence regarding the reduction of the likelihood of early dropout from treatment. In turn, olanzapine associated with fluoxetine was not superior to fluoxetine alone in patients who did not respond to venlafaxine when assessing the average score of the Montgomery-Asberg (MADRS) depression rating scale, either in the remission or in the response rates¹¹³.

A final study randomised non-responder patients after eight weeks of treatment with fluoxetine into groups with an increase of the fluoxetine dose, with a combination of fluoxetine and olanzapine and with olanzapine alone at different doses. The authors found significant differences in favour of the association antidepressant and olanzapine in terms of an average variation of the MADRS score and also in secondary measurements such as the remission and response rates. However, the dropout rates were higher with the combination of fluoxetine and olanzapine¹¹⁴.

Summary of the evidence

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

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

Recommendations

✓	In patients with a partial response at the third or fourth week of treatment, it is advisable to: <ul style="list-style-type: none"> - Wait for the clinical evolution until week eight. - Increase the dose of the drug up to the maximum therapeutic dose.
✓	For a patient who does not improve with the initial pharmacological treatment for depression, it is advisable to: <ul style="list-style-type: none"> - Revise the depressive disorder diagnosis. - Verify that the treatment is being followed. - Confirm that the antidepressant is being taken at the right time and dose.
B	If the patient does not improve at the third or fourth week, any of the following strategies could be followed: <ul style="list-style-type: none"> - Switching from an antidepressant to any family, including another serotonergic. - Combining antidepressants. - Augmenting the initiated treatment with lithium or triiodothyronine.
B	It is not advisable to increase the dose of an SSRI if there is no response after three weeks of treatment.

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