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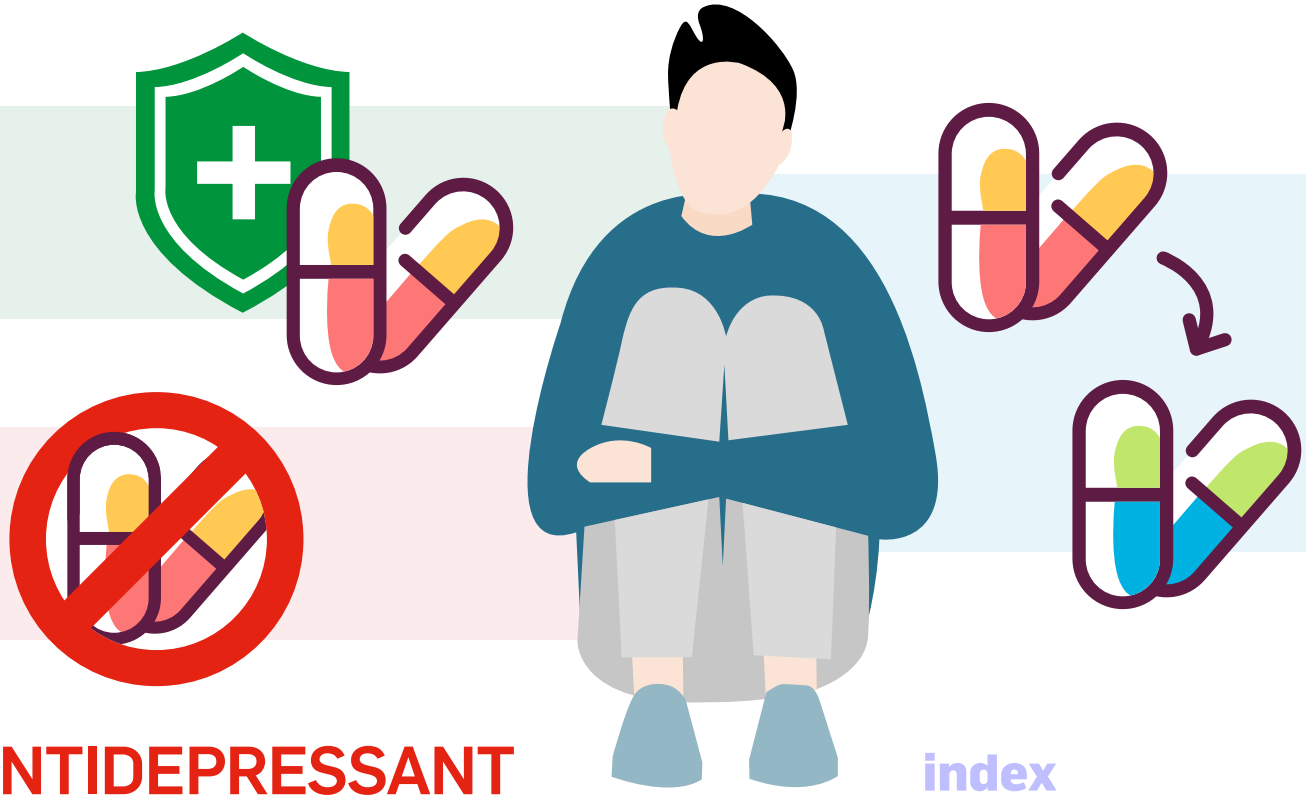

ANTIDEPRESSANT SAFE USE, DEPRESCRIPTION AND SWITCHING GUIDELINE

INTRODUCTION Antidepressant use has increased over the past few years. Given the lack of evidence concerning differences in efficacy between the various antidepressants, it is important to understand the safety profile to ensure the safe use thereof. Antidepressant treatment typically lasts for too long, partly due to the absence of specific deprescription guidelines. An understanding of the best methods for switching between antidepressants, and the most suitable methods for deprescribing, may help to optimise the pharmacotherapy of depression. OBJECTIVES To establish suitable guidelines for the prescribing, switching, use and deprescribing of antidepressants. METHODS A search was carried out for clinical practice guidelines, systematic reviews and bulletins to compile the evidence available regarding the correct use and deprescribing of antidepressants. The prescription database of the Servicio Navarro de Salud-Osasunbidea (SNS-O) [Navarre Health Service] was used to obtain data regarding antidepressant use in Navarre.CONCLUSIONS When planning the treatment of depression it is necessary to consider, initially, whether the prescription of an antidepressant drug is actually indicated in that specific situation. Secondly, it is crucial to think about the characteristics and comorbidities of the patient when selecting the most appropriate drug. In this regard, before adding a new drug, pharmacotherapy must be optimised by increasing the dose, waiting for the appropriate amount of time and considering switching to another antidepressant. Finally, treatment must be reassessed periodically considering that such treatments are not for life and withdrawal of the drug gradually and with the patient's consent should be evaluated to increase the likelihood of a successful withdrawal.

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INTRODUCTION

According to the report on the use of antidepressants in Spain published by the Spanish Agency for Medicines and Medical Devices (AEMPS) in 2015, depression has a lifetime prevalence of 10.5%, with this figure being higher for women (14.4%) than for men (6.2%), and a one-year prevalence of 4%[1].

According to the same report, antidepressant use in Spain increased by 200% over the period 2000-2013[1]. This increase may be due to factors such as a change in the psychiatric care model, with a more relevant role for Primary Care, which has facilitated access to treatments, the approval of new drugs or new indications for previous drugs, and the medicalisation of society, which has resulted in an increase in the demand for pharmacological resources to treat personal and social conditions that often lack an underlying pathological condition[2]. Moreover, the lack of specific deprescribing guidelines leads to the prolongation of these treatments over time.

OBJECTIVES

A document with three main objectives was drafted by a multidisciplinary working group comprising mental health, primary care and pharmacy professionals:

- To establish basic criteria for the safe use of antidepressants depending on the characteristics of the drug concerned and the patient.
- To establish a series of antidepressant deprescribing criteria, both general and specific for each type of antidepressant.
- To establish criteria of switching between antidepressants.

This bulletin has been drafted on the basis of that document, so it will highlight some general considerations regarding the safe use of antidepressants, describe when and how an antidepressant should be deprescribed and how to switch between antidepressants, when required.

EVOLUTION OF ANTIDEPRESSANT USE (2015–2019) AND THE CURRENT SITUATION

The number of patients treated with antidepressants in Navarre in the period 2015-2019 (pre-pandemic) increased by 10.2%, whereas the number of DDDs (Defined Daily Dose) increased by 11.7%.

In terms of therapeutic groups, we found that consumption during this period was higher in the group of "other antidepressants", with an increase of 14.3% in the DDDs invoiced, compared with 10.4% in the case of selective serotonin reuptake inhibitors (SSRIs) and 6.7% in the case of tricyclic antidepressants (TCAs). Monoamine oxidase inhibitors (MAOIs) were not considered in this bulletin as their use is currently very limited.

The group of "other antidepressants" includes the following: mianserin, trazodone, mirtazapine, bupropion, venlafaxine, desvenlafaxine, reboxetine, duloxetine, vortioxetine, tianeptine and agomelatine.

In terms of active substance (Fig. 1), whereas the consumption of some drugs remains relatively stable, the increase in the use of tianeptine* (1180%), vortioxetine* (353%), desvenlafaxine (86%), sertraline (36%), and trazodone (28%), should be noted, as should the decrease in the use of doxepin (-56%).

Figures 2 and 3 show that, in 2019, 49% of antidepressants prescribed were SSRIs, with escitalopram being the most widely prescribed active substance (37%), followed by sertraline (24%).

(*) Increases in the consumption of tianeptine (1180.65%) and vortioxetine (353.33%) have been excluded from the figure. Vortioxetine was first used in 2016. The decrease in the consumption of mianserin and maprotiline has also been excluded as these values are not representative due to supply problems.

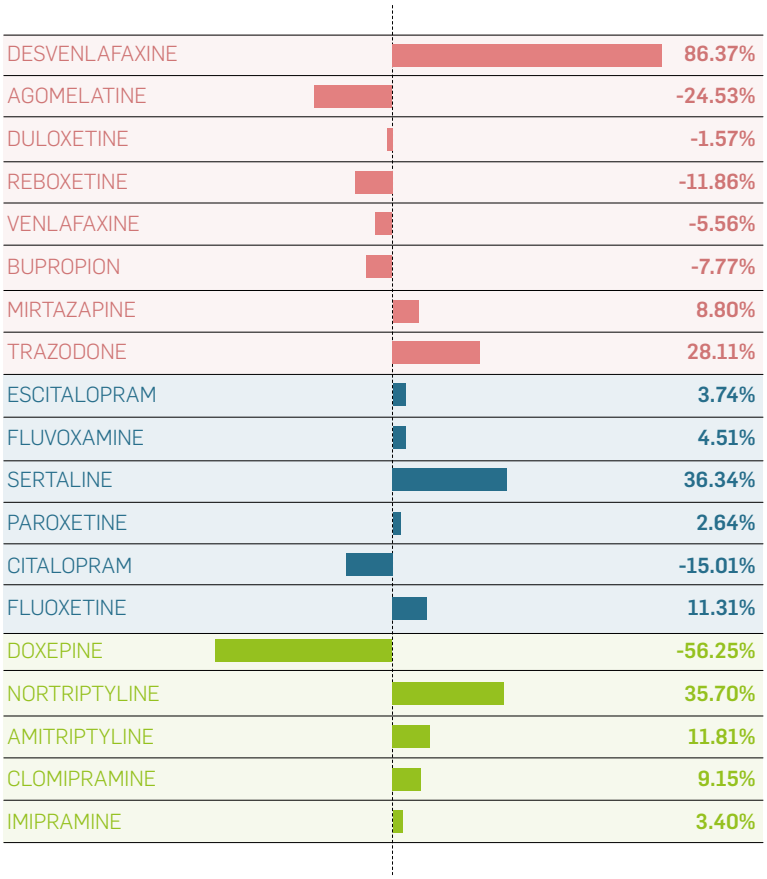

Figure 1. Change in DDDs invoiced in the period 2015–2019, ordered by therapeutic group.

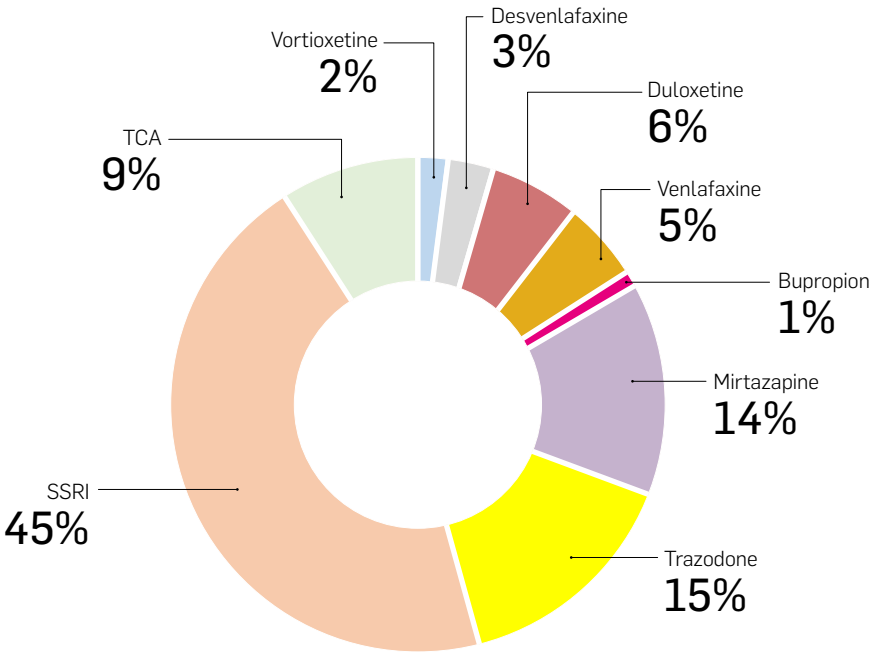

Figure 2. Distribution of patients treated with the different antidepressants in Navarre in 2019.

TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor.

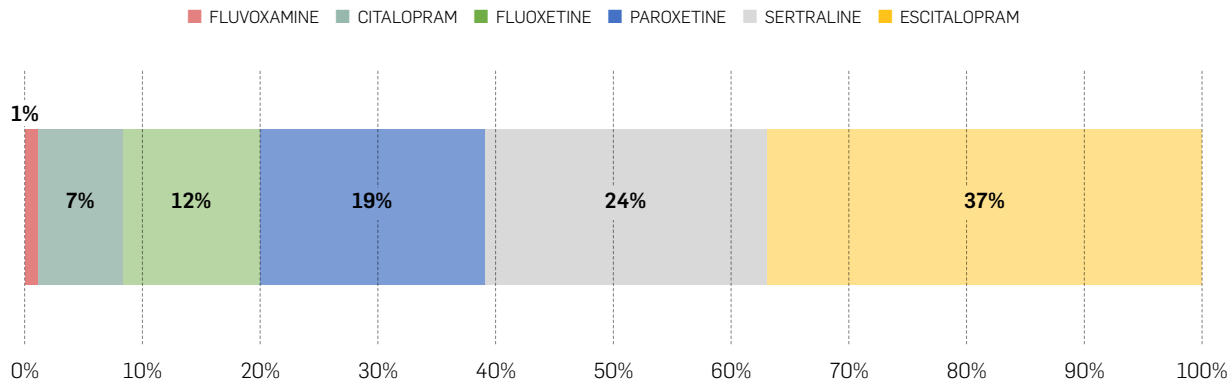

Figure 3. Distribution of patients treated with selective serotonin reuptake inhibitors in Navarre in 2019.

PRESCRIPTION OF ANTIDEPRESSANTS

The psychotherapeutic treatment of depressive disorders in primary care can improve the quality of life for many patients, especially those suffering from mild to moderate disorders, without needing any form of pharmacological treatment[3]. In general, the use of antidepressants is not recommended for mild depression as the risk-benefit relationship is unfavourable. Pharmacological treatment is only considered in cases of mild depression when this could complicate the management of other comorbidities[4].

It is recommended to offer support to patients and their families to develop coping strategies and inform them about non-pharmacological alternatives, such as psychological, social, counselling and support therapy.

After performing an appropriate clinical interview, some general principles can be applied[3]:

- Initiate, develop and maintain an appropriate clinical relationship: closeness, empathy and emotional support.
- Provide the patient with psychotherapeutic strategies and education regarding self-help skills: relaxation techniques, training in problem solving, support to establish goals and life plans, promote physical activity and information regarding sleep hygiene.
- Inform patients about the therapeutic plan and promote their participation in treatment.
- Monitor patient's progress. Decide whether to prescribe treatment or refer to mental health in the event of no improvement. If improvement is noted, re-assess the need for treatment after a period of time.

Pharmacological treatment is considered to be the first-line for moderate and severe depression and should also be considered in other situations, such as[4]:

There are no marked efficacy differences between TCAs and SSRIs, or between the different SSRIs

- Minor depression whose symptoms persist for at least 2 years.
- Minor or mild major depression that persists after having performed other non-pharmacological interventions, such as low-intensity psychological treatments based on the principles of cognitive behavioural therapy, previously.
- Patients with a history of moderate or severe depression.

SAFE USE OF ANTIDEPRESSANTS

The lack of marked differences in terms of efficacy between TCAs and SSRIs[5–7], as well as between the different SSRIs[6–8], means that the antidepressant should be chosen based on the safety profile of each drug, the patient's comorbidities and treatment costs.

Tricyclic antidepressants (TCAs)

The most common adverse effects of tricyclic antidepressants are anticholinergic effects, both central (cognitive, attention and memory alterations, dizziness,

instability, confusion and delirium) and peripheral (constipation, urinary retention, glaucoma, blurred vision and dry mouth), adverse cardiovascular effects and, to a lesser extent, weight gain and sexual dysfunction.

These drugs have also been related to a higher toxicity and risk of death in the event of overdose[4].

Given their adverse effects profile, TCAs are only indicated on severe and/or refractory depression (when others are ineffective or are not tolerated) or when other indications justify their use[4,9].

Anticholinergic burden

The anticholinergic burden of a treatment is the result of the combined effect of taking one or more drugs with anticholinergic activity[10]. Exposure to a high anticholinergic burden has been related to important risks, such as falls, cognitive impairment, worsening of cardiovascular function and increased mortality[11,12].

Various scales have been developed to measure the anticholinergic burden due to a treatment. These scales classify drugs on the basis of their anticholinergic potential, assigning a score to each.

The scores assigned to various antidepressants, depending on the scale used, are shown in Table 1. It can be seen that TCAs (amitriptyline, clomipramine and imipramine) have the highest anticholinergic burden. Moreover, it should be noted that paroxetine is the SSRI with the largest anticholinergic effect.

The antidepressant should be selected on the basis of the adverse effects profile for each drug and the patient's characteristics

TCAs are only indicated for severe and/or refractive depression or when other indications justify their use

As a prescribing aid, the Navarre Health Service has incorporated into its electronic prescribing software the item "anticholinergic burden"which, using the ACB scale, calculates the anticholinergic burden of the treatment for all patients. .

Table 1. Anticholinergic burden assigned to the main antidepressants using different scales.

	SCALES								
Drug	**ACB**	**ARS**	**CHEW**	**ADS**	**ASA**	**ALS**	**CrAS**	**DURAN**	**ABC**
Bupropion	1	0	0	0	0	0	1	0	0
Duloxetine	0	0	1	0	0	0	0	0	0
Amitriptyline	3	3	4	3	4	3	3	2	3
Citalopram	0	0	2	1	2	1	0	1	0
Clomipramine	3	0	0	3	0	0	0	2	3
Fluoxetine	0	0	2	1	2	1	1	1	0
Imipramine	3	3	0	3	0	3	3	2	3
Mirtazapine	0	1	2	1	0	0	0	1	0
Paroxetine	3	1	3	2	3	2	2	1	0
Sertraline	0	0	0	1	0	0	1	0	0
Venlafaxine	0	0	0	0	0	1	1	0	0

ACB: Anticholinergic Cognitive Burden Scale, ARS: Anticholinergic Risk Scale, CHEW: Chew's scale, ADS: Anticholinergic Drug Scale, AAS: Anticholinergic Activity Scale, ALS: Anticholinergic Load Scale, CrAS: Clinician-Rated Anticholinergic Scale, DURAN: Duran's scale, ABC: Anticholinergic Burden Classification.

According to this scale, drugs with a score of 2 or 3 may increase the risk of cognitive impairment by 46% over 6 years[11]. In addition, for each one-point increase in the total score, the score for the mini-mental state examination (MMSE) decreased by 0.33 points over 2 years and the anticholinergic burden was correlated with an increased risk of death[12].

With regard to the anticholinergic burden:

- Special care must be taken in elderly patients.
- Special care must be taken in patients with risk diagnoses: institutionalised patients, those with a risk of fall or previous falls, mobility and/or balance alterations, vertigo, cognitive impairment or dementia, glaucoma, constipation or episodes of urinary retention.
- See the STOPP criteria for TCAs[13].

Cardiovascular safety

TCAs may cause arrhythmias, blockades, sinus tachycardia, worsening of previous heart failure and alterations to the ECG (T-wave flattening, ST segment depression and QRS broadening)[4].

TCAs may also cause orthostatic hypotension[4].

With regard to cardiovascular safety:

- Care should be taken in patients with recent acute myocardial infarction (AMI), with any degree of heart block or with heart rhythm disorders and chronic ischaemic heart disease.
- See the STOPP criteria for TCAs[13].

Selective serotonin reuptake inhibitors (SSRIs)

These are associated with fewer anticholinergic side-effects and a lower probability of causing postural hypotension or sedation. They are less cardiotoxic and safer than TCAs in the event of overdose. The adverse effects of SSRIs include: serotonin syndrome, prolonged QT interval, increased risk of bleeding, hypernatraemia, increased risk of suicide, psychiatric alterations and sexual dysfunction.

There is currently no evidence for the clinical superiority of any single SSRI over any other[6–8], therefore the drug should be selected based on factors such as age, history of good response or differences in the incidence of certain adverse reactions, as well as the cost. With regard to the interactions, it should be noted that fluoxetine, fluvoxamine and paroxetine are the SSRIs with the higher potential interactions, whereas citalopram and sertraline present a lower risk in this regard[4].

SSRIs are the antidepressants with the greatest evidence for their safety and efficacy, and with the best risk-benefit balance: first choice[4].

Citalopram and escitalopram are the most selective inhibiting serotonin reuptake.

Fluoxetine has a long half-life and may therefore cause problems when switching to another antidepressant if a wash-out period is not applied[4].

Fluvoxamine is associated with a higher incidence of nausea than other SSRIs, thus limiting its use in clinical practice[4].

Paroxetine is associated with a higher rate of treatment withdrawals due to adverse effects than other SSRIs. It also presents a higher incidence of sedation and sexual dysfunction that other SSRIs[4].

STOPP criteria for TCAs

DEMENTIA Risk of worsening of the cognitive status.
GLAUCOMA Possible worsening of the glaucoma.
HEART CONDUCTION DISORDERS Pro-arrhythmia effects.
CONSTIPATION Possible worsening of constipation.
LOWER URINARY TRACT SYMPTOMS OR HISTORY OF URINARY RETENTION Risk of urinary retention.
USE WITH OPIOIDS OR CALCIUM ANTAGONISTS Risk of severe constipation.

Sertraline is well tolerated. It also has a higher probability that efficacy improves at higher doses compared with other SSRIs[14].

Serotonin syndrome

Numerous antidepressants can provoke serotonin syndrome when administered concomitantly with other drugs with similar activity, such as dextromethorphan, tramadol, 5-HT1 agonists ("triptans"), lithium, antiemetics (metoclopramide, ondansetron, granisetron) and anti-Parkinson drugs (selegiline, rasagiline)[15,16].

Serotonin syndrome comprises three groups of symptoms, although all three do not necessarily have to appear, and its severity varies from mild to potentially fatal. These symptoms are[17]:

- Mental alterations: anxiety, restlessness, disorientation, agitation, excitation.
- Neuromuscular problems: clonus (repetitive muscle spasms or contractions, often rhythmic), tremor, hyperreflexia, muscle stiffness.
- Autonomic hyperactivity: hypertension, tachycardia, tachypnoea, hyperthermia, mydriasis, diaphoresis, mucosal dryness, reddened skin, tremor, vomiting, diarrhoea, increased peristalsis, arrhythmias.

The onset of symptoms is usually rapid, often a few hours after starting the drug or changing the dose, and many cases resolve within the 24 hours following suspension of the serotonergic drug[17].

The University of Waterloo classifies the drugs that can produce serotonin syndrome into two groups (Table 2)[18].

A series of recommendations to be taken into consideration when combining various of these drugs was proposed based on this classification[18]:

- **Avoid** concomitant treatment with several MAOIs (group A) or with an MAOI and other drugs that increase serotonin levels (group B).
- **Take care** in the event of concomitant treatment with two or more drugs from group B (especially if one of them is prescribed at high doses).
- **Remain alert** when a drug from group B is added to treatment with another drug from group B. It is recommended to start with low doses, increasing the dose slowly and monitoring for the onset of symptoms.

SSRIs and the first-choice antidepressants

QT interval prolongation and heart disease

Prolongation of the QT interval is a dose-dependent effect that favours the onset of heart arrhythmias, such as torsades de pointes, the risk of sudden death and, possibly, other ventricular arrhythmias under some circumstances[19].

In 2011 the AEMPS issued an alert limiting the doses of citalopram and escitalopram to be administered and contraindicating their use in patients with congenital long QT syndrome or a history of QT prolongation and concomitant treatment with other drugs that prolong the QT interval[19,20]. In general, citalopram dose is limited to 40 mg per day, although it is restricted to 20 mg in patients older than 65 years and those with liver disease. The maximum dose in the case of escitalopram is 20 mg, decreasing to 10 mg in patients older than 65 years. These restrictions may affect the effectiveness of antidepressant treatment[21].

Fluoxetine should also be used with care in patients with long QT syndrome or a family history of QT prolongation[22].

In the case of fluvoxamine and paroxetine, care should only be taken in the event of concomitant administration with drugs that prolong the QT interval[22].

Although sertraline can also produce a prolongation of the QT interval[22], there is some evidence that this is a safer alternative for the treatment of recurrent depression in patients who have suffered a recent AMI or with unstable angina[23–26]. Sertraline is considered to be the most appropriate SSRI in patients with heart disease[27].

Antidepressant treatment should only be initiated 6 weeks after an AMI, except in the case of depression with suicidal ideation or the onset of depressive symptoms in a patient with a history of severe depression during hospitalisation[26].

Table 2. Classification of drugs based on their ability to cause serotonin syndrome.

Group A	Group B
Irreversible, non-selective MAOIs: Phenelzine	**Antidepressants:** • SSRIs: paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine. • SNRIs: venlafaxine, desvenlafaxine, duloxetine. • TCAs: clomipramine, imipramine.
Reversible, non-selective MAOIs: Linezolid	**Opioids:** Tramadol, meperidine, methadone, fentanyl.
Selective and reversible MAOB inhibitors: Selegiline, rasagiline	**Antitussives and antihistamines:** Dextromethorphan, chlorpheniramine.
Selective and reversible MAOA inhibitors: Moclobemide	**Others:** • Triptans. • Other antidepressants: mirtazapine and trazodone. • Antiemetics: 5HT-3 antagonists (ondansetron) and metoclopramide. • Buspirone, lithium.

MAOI: monoamine oxidase inhibitors; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin norepinephrine reuptake inhibitors; TCAs: tricyclic antidepressants; MAOA: monoamine oxidase A; MAOB: monoamine oxidase B.

The following is recommended with regard to heart disease and prolongation of the QT interval:

- Avoid citalopram and escitalopram in patients with heart disease.
- The use of sertraline as an SSRI is preferred in patients with heart disease.
- Wait for 6 weeks before prescribing an SSRI after an AMI.

Anticholinergic burden

Although anticholinergic effects are not the main adverse effect to be be considered with SSRIs, paroxetine is known to have a marked anticholinergic effect.

The following is recommended with regard to the anticholinergic burden:

- Avoid paroxetine in the elderly and in patients who may worsen if the anticholinergic effect increases (constipation, urinary retention, falls, confusion).

Haemorrhage

The majority of bleeding episodes caused by SSRIs are minor (petechiae, epistaxis, haematoma, etc.) and resolve after withdrawal of the drug. However, cases of digestive and intracranial haemorrhage have been reported, especially in elderly patients. Such haemorrhages typically occur at the onset of treatment and the risk is greater if the patient is also taking other drugs that increase the risk of bleeding, such as non-steroidal anti-inflammatories (NSAIDs)[28] and oral anticoagulants. One study found that SSRIs increase the risk of digestive bleeding 2.6-fold, and that the risk increases 15-fold in patients treated simultaneously with SSRIs and NSAIDs. This increase in risk did not vary with age, sex, dose or duration of treatment[29,30].

Cases of vaginal bleeding, increased risk of perioperative bleeding, haematomas and haemorrhage in children born to mothers treated with SSRIs have also been reported[31].

Since 2020, the summary of product characteristics for SSRIs and SNRIs include the warning of a higher risk of postpartum haemorrhage with the use of antidepressants in pregnant women as a result of a recommendation from the European Pharmacovigilance Risk Assessment Committee (PRAC).

With regard to the risk of haemorrhage, we recommend:

- To prescribe SSRIs with caution in patients being treated with anticoagulants.
- Prophylaxis with proton-pump inhibitors (PPIs) in patients older than 65 years, even in the absence of a prior history of gastroesophageal reflux disease or gastrointestinal ulcer, when receiving concomitant treatment with antiaggregants, NSAIDs, anticoagulants or corticosteroids[32].

Hyponatraemia

Hyponatraemia is defined as a serum sodium concentration of <135 mmol/L and is the most common fluid and electrolytic disturbance in clinical practice[33].

SSRIs increase the release/sensitivity of antidiuretic hormone (ADH), thus leading to an increased risk of hyponatraemia. This mainly occurs during the first month of treatment, irrespective of the drug dose. The symptoms include dizziness, drowsiness, lethargy, confusion, muscle cramps, seizures and cognitive impairment. The intensity of these symptoms varies but can lead to the death of the patient. This effect normally resolves two weeks after withdrawal of the drug[34].

Special care must be taken in patients presenting risk factors such as advanced age, female, low weight, treatment with diuretics or antiepilepsy drugs, prior history of hyponatraemia, renal impairment and alcoholism. Plasma sodium levels should be monitored during the first few weeks of treatment, especially in those patients with risk factors for hyponatraemia[34].

In a study that analysed the onset of hyponatraemia in 72,509 patients treated with different antidepressants, the only antidepressant that was not associated with the onset of hyponatraemia was mianserin. The highest incidence rate ratio (compared with the period prior to use) was for citalopram (7.8; 95% CI: 7.42-8.20), whereas the lowest value was for venlafaxine (2.90; 95% CI: 2.43-3.46) and mirtazapine (2.95; 95% CI: 2.71-3.21)[35].

Amongst SSRIs, the highest probability of suffering hyponatraemia was found for fluoxetine, citalopram and escitalopram[36].

With regard to the risk of hyponatraemia, we recommend:

- Avoiding the use of fluoxetine, citalopram and escitalopram in patients with a risk of suffering hyponatraemia. If used, monitor sodium levels at the onset of treatment.
- See the STOPP criteria for SSRIs[13]:

SNRIs should be reserved for patients who do not respond to SSRIs or who do not tolerate them

Hyperglycaemia

SSRIs may affect glycemic control, therefore an adjustment to the dose of insulin and/or other hypoglycaemia medications used concomitantly may be required.

"Dual" serotonin norepinephrine reuptake inhibitors (SNRIs)

Dual antidepressants (venlafaxine, desvenlafaxine and duloxetine) do not exhibit clinically significant advantages in terms of efficacy with respect to either SSRIs or other antidepressants, therefore they are considered to be second-line antidepressants[9]. They present a similar safety profile to SSRIs, although at high doses they can be cardiotoxic due to their noradrenergic action[4] (hypertension, prolongation of the QT interval), therefore they should be used with care in hypertense patients and in those with glaucoma[3].

The frequency of treatment interruption due to adverse effects is higher for duloxetine and venlafaxine than for the majority of SSRIs[4,37,38].

They have not shown to be more effective or safer than SSRIs, therefore their use should be reserved for patients who do not respond to SSRIs or who do not tolerate them.

STOPP criteria for SSRIs

History of clinically significant hyponatraemia (Na<130 mmol/L not iatrogenic in the previous two months).

Venlafaxine is associated with a higher risk of death in the event of overdose than for SSRIs[4]. The risk of bleeding is higher and the use thereof has been linked to dose-dependent increases in blood pressure and heart rate and to a clinically relevant increase in serum cholesterol levels. As such, blood pressure and cholesterol levels should be monitored in at-risk patients, and these drugs should be used with care in patients with a recent AMI, unstable heart disease and in those with an elevated risk of cardiac arrhythmias[22].

Desvenlafaxine is an active metabolite of venlafaxine and there are no studies comparing the two. It can cause an increase in blood pressure and cholesterol levels, headache, insomnia, sexual dysfunction and weight gain[22].

Duloxetine has been associated with an increase in blood pressure[22,39]. Cases of hypertensive crisis have been reported, especially in patients with pre-existing hypertension. In a placebo-controlled study involving patients with no severe or uncontrolled medical conditions, in addition to an increase in blood pressure, an increased heart rate was observed with duloxetine, although no clinically relevant changes were observed in the electrocardiogram at the approved dose of 60 mg/day[39]. Increase in total cholesterol, bleeding, gastrointestinal disorders and hepatotoxicity may also appear[22].

Given the above adverse effects profile, we recommend:

- Avoiding SNRIs in uncontrolled hypertense patients with altered heart rhythm or with a recent AMI.

Other antidepressants

Trazodone has a pronounced sedative effect that may be useful when administered at low doses. Heart conduction disorders, ventricular arrhythmias and orthostatic hypotension may occur at doses higher than 200 mg/day. Priapism is an uncommon side-effect[26].

Mirtazapine is widely used in the elderly at low doses due to its sedative effect. It causes an increase in appetite and weight. It should be used with care in patients with heart diseases such as conduction disorders, angina pectoris and recent myocardial infarction, as well as in patients with diabetes mellitus[22].

Agomelatine may cause elevated transaminase levels, hepatitis and hepatic impairment. In this regard, in 2014 the AEMPS issued an alert recommending not to start new treatments in patients aged more than 75 years and to monitor liver function in all patients so that it could be suspended if liver enzyme values exceeded three times the upper limit of normal[40]. It may also cause weight gain and suicidal ideation.

Bupropion may cause neuropsychiatric effects such as mania and bipolar disorder, severe allergic reactions, dose-dependent seizures (it is contraindicated in patients with current convulsive disorder or a history of seizures) and congenital defects[22]. It has a favourable cardiovascular side-effects profile, although arterial hypertension, which may, on occasion, be severe and require intensive treatment[26]. Baseline blood pressure should be monitored at the start of treatment and subsequently followed-up, especially in patients with hypertension[22].

Vortioxetine has not been compared with the antidepressants of choice. There is no evidence for an equal or greater efficacy versus SSRIs or SNRIs and it has not always been found to be more effective than placebo[41]. There is no evidence of a greater efficacy versus other SSRIs in the improvement of cognitive impairment. As far as safety is concerned, its profile is similar to that for other SSRIs or SNRIs, except for nausea. It can be withdrawn immediately.

Tianeptine is a TCA that it is not authorised in the majority of the Western world and has been recalled from the market in other countries. It can cause hepatitis, severe skin reactions and is highly addictive[42].

Reboxetine causes a decrease in potassium levels in the elderly, insomnia, constipation, sweating, dry mouth, dizziness, headache, decreased appetite and seizures. Cases of elevated heart rate have been reported[22].

Compared with other antidepressants, **mianserin** has the advantage of lacking anticholinergic activity and causing fewer cardiovascular effects. Its main disadvantage is that it can produce blood dyscrasias (agranulocytosis) and seizures, prolongation of the QT interval and sedation[22].

Adverse effects common to the different groups of antidepressants

Central Nervous System side effects

Headache, dizziness and insomnia are the most common adverse reactions associated with SSRIs, SNRIs and "others" antidepressants (Table 3).

Sexual dysfunction

Patients with depression often present some degree of sexual dysfunction, which may be caused by the disease itself and/or the use of antidepressants. Those antidepressants with the highest serotonergic selectivity appear to be associated with higher rates of sexual

Table 3. Incidence of Central Nervous System-related adverse reactions with the different antidepressants37.

	Incidence % (95% CI)		
	Dizziness	**Headache**	**Insomnia**
Citalopram	9.1% (3.7-14.4)	14.3% (7.8-20.7)	6.9% (1.4-12.5)
Escitalopram	1.3% (0-14.3)	7.4% (3.3-11.5)	6.9% (1.3-10.8)
Fluoxetine	7.6% (6.2-9.0)	21.3% (16.3-26.3)	13.8% (11.4-16.2)
Fluvoxamine	18.3% (0-62.4)	20.1% (3.3-36.8)	24.2% (0.3-48.0)
Paroxetine	0.8% (0-2.9)	3.2% (0-8.1)	12.7% (9.9-15.4)
Sertraline	8.5% (5.9-11.2)	19.8% (14.9-24.7)	9.8% (6.1-13.6)
Venlafaxine	4.3% (0-13.8)	19.3% (13.9-24.7)	17.8% (12.2-23.2)
Duloxetine	41.5% (8.1-91.0)	15.8% (3.9-27.7)	16.6% (14.1-19.1)
Bupropion	11.6% (2.2-21.1)	28.6% (23.2-34.1)	15.7% (10.9-20.6)
Mirtazapine	8.4% (4.6-12.1)	12.1% (10-14.3)	8.0% (1.8-14.3)

dysfunction, whereas those with a more favourable sexual profile tend to be non-serotonergic[43]. Comparing between SSRIs, paroxetine produces more frequently sexual dysfunction[45] (Table 4).

Suicide risk

A dysphoric state, characterised by physical disinhibition and the onset of anxiety, irritability, hostility and impulsiveness, may occur in the first few weeks after the start of antidepressant treatment. This, together with the suicide risk associated with the disease itself, may result in an increase in suicide-related ideas or behaviours. If these symptoms are intense or prolonged, start suddenly or are not related to the initial symptoms, antidepressant treatment may need to be suspended[4].

Suicidal tendencies associated with antidepressant use in children and adolescents have been the focus of numerous studies, and several regulatory agencies and organisations have published reviews in this regard[46,47], the results of which have led the Food and Drug Administration (FDA) and other regulatory agencies to issue communiques warning of the risk of antidepressant use in this population. The AEMPS also issued several alerts in this regard in 2004 and 2005[49], and does not recommend the use of SSRIs or SNRIs in children and adolescents outside the authorised indications.

The risk of suicidal ideation in children and adolescents is more than threefold higher with SSRIs or SNRIs in comparison with placebo. Based on observational evidence, SSRIs increase the risk of suicide[49].

Table 4. Prevalence of sexual function-related adverse effects for antidepressants45.

Drug	Prevalence	Comments
TCA	30%	Decreased libido, erectile dysfunction, delayed ejaculation and ejaculation alterations.
SSRIs	60-70%	Paroxetine is associated with greater erectile dysfunction and vaginal dryness than other SSRIs.
Venlafaxine	70%	Decreased libido, erectile dysfunction and delayed ejaculation.
Duloxetine	46%	May affect all phases of the sexual response.
Mirtazapine	25%	Decreased libido, erectile dysfunction and delayed ejaculation or absence thereof.
Buproprion	22-25%	Ejaculation alterations, decreased libido.
Reboxetine	5-10%	Ejaculation alterations.

TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors.

Fluoxetine is the only drug approved for the treatment of depressive disorder in children and adolescents[22].

Sertraline is indicated to treat obsessive-compulsive disorder in patients aged 6 to 17 years[22].

Selection criteria

Consequently, considering the safety aspect to be a priority when selecting the most appropriate antidepressants, Table 5 summarises the most indicated antidepressants given possible patient comorbidities.

Table 5. Antidepressants of choice depending on comorbidities[27,50,51].

CONDITION	✓	✗
DEMENTIA	SSRI (citalopram). If associated insomnia; mirtazapine and trazodone.	Avoid TCAs.
HEART DISEASE	Sertraline.	Avoid TCAs and SNRIs. Citalopram and escitalopram for prolongation of the QT interval. Trazodone after recent AMI.
GLAUCOMA	SSRIs (fluoxetine, sertraline).	Avoid TCAs. Caution with venlafaxine and duloxetine.
HYPERTENSION	SSRIs.	Avoid dual antidepressants (duloxetine, venlafaxine and desvenlafaxine) and buproprion
BENIGN PROSTATE HYPERPLASIA	SSRIs (fluoxetine, sertraline and citalopram).	Avoid TCAs.
CHRONIC PAIN	Sedative antidepressants and/or with analgesic effect such as amitriptyline. Duloxetine in diabetic neuropathy.	Caution when using NSAIDs with SSRIs.
EPILEPSY	SSRIs, monitoring possible onset of seizures.	Do not use buproprion (contraindicated). Avoid TCAs (clomipramine and maprotiline). Caution with venlafaxine, duloxetine, mirtazapine, reboxetine.
MIGRAINE	Amitriptyline.	Avoid concomitant use with triptans.
OBESITY	Fluoxetine, buproprion. Paroxetine: greater weight gain than for other SSRIs.	Avoid TCAs and mirtazapine.
PARKINSON'S DISEASE	Sertraline, buproprion, nortriptyline.	Caution with SSRIs, especially paroxetine and fluoxetine.
INSOMNIA	Trazodone, mirtazapine.	Avoid buproprion.
SPECIAL SITUATIONS	✓	✗
ELDERLY PATIENTS	Sertraline, mirtazapine, citalopram (care with possible QT prolongation).	Avoid paroxetine and TCAs.
CHILDREN AND ADOLESCENTS	Fluoxetine.	
PREGNANCY	Fluoxetine (consider withdrawing in the third trimester) or sertraline.	Avoid paroxetine.
BREAST-FEEDING	Paroxetine or sertraline.	

SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants; AMI; acute myocardial infarction; NSAID: non-steroidal anti-inflammatory drug; SNRIs: serotonin norepinephrine reuptake inhibitors.

DEPRESCRIBING ANTIDEPRESSANTS

Deprescribing is defined as the withdrawal of unsuitable drugs supervised by a medical professional[52]. The aim is to reconsider treatment from the beginning, starting with an understanding of the patient's state and situation to the diagnosis of their health problems, indication of the necessary drugs and subsequent follow-up. It is a continuous process (prescribing/deprescribing)[53].

In the specific case of antidepressants, the lack of specific deprescribing guidelines leads to a prolongation of treatments, thus contributing to a higher number of patients in treatment. Consequently, physicians should be particularly aware of this and attempt to minimise the duration of treatments, closely following the summary of product characteristics and antidepressant use guidelines. Moreover, it is essential that the deprescribing process is agreed upon with the patient.

In 2021, Cochrane reviewed the evidence available concerning the effectiveness and safety of the various deprescribing guidelines available compared with continued, long-term use of antidepressants for depressive and anxiety disorders in adults. This review concluded that few studies are available, and therefore that no firm conclusions can be drawn regarding the effectiveness and safety of such guidelines. Moreover, these studies contain biases by identifying withdrawal symptoms as relapse, and the deprescribing periods are limited to no more than four weeks. This review states that future studies should include key outcomes such as the successful interruption rate and should include populations with one or no prior episode of depression in primary care, elderly subjects and subjects taking antidepressants for anxiety, and should use gradual reduction schemes lasting for more than four weeks[54].

Deprescribing should be considered if:

- There is low treatment adherence.
- The patient requests it.
- Treatment is ineffective: after a first antidepressant treatment, around 38% of patients with major depression do not respond to a second drug after treatment for 6-12 weeks, and 54% do not achieve remission[44].
- Adverse effects such as hyponatraemia, prolongation of the QT interval, anticholinergic symptoms, bleeding, etc., appear.
- They are used to manage the behavioural symptoms of Alzheimer's disease (LESS CHRON criteria)[55].

Special attention must be paid to the cardiovascular effects of antidepressants

The lack of specific deprescribing guidelines leads to the prolongation of these treatments over time

- After the following times[27]:
  - » 6 months after remission of a first depressive episode
  - » 12 months after the remission of a second depressive episode
  - » 24 months after the remission of a third or subsequent episode

Patients with certain risk factors may require long-term, and occasionally lifetime, antidepressant treatment[56].

- Elderly.
- Recurrent episodes (three or more episodes).
- Chronicity or with associated psychotic symptoms.
- Severe episodes or difficulty treating episodes.
- Significant comorbidity (mental or physical).
- History of relapse after stopping antidepressant treatment.

When deprescribing one or more antidepressants, the physician should initially evaluate whether the original purpose for which it was prescribed has been achieved. If it is being used for other indications, such as insomnia, neuropathic pain or migraine, it should be evaluated whether that indication remains valid before deprescribing.

General guidelines for deprescribing

Treatment should be withdrawn gradually to avoid the onset of withdrawal syndrome, the symptoms of which are known as FINISH SYNDROME[57]. It is important to inform patients about these symptoms so that they can identify them:

- **F** *Flu-like* symptoms (fatigue, lethargy, myalgia, chills).
- **I** Insomnia.
- **N** Nausea.
- **I** Instability (dizziness, vertigo, ataxia).
- **S** Sensory (disorders): paresthesia, sensations of electric shock.
- **H** Hyperactivity (restlessness, agitation, anxiety).

Withdrawal syndrome when stopping antidepressant use has been overlooked for a number of years. Initially the symptoms were described as being mild, resolved alone in 1-2 weeks and only intense in a limited number of cases. However, there is now evidence that withdrawal syndrome is more common than initially thought, that it can last for several months, and is often serious[58].

The first systematic review of withdrawal syndrome in antidepressants was published in 2015 (20 years after SSRIs were released to market). The four systematic reviews of this topic currently available agree that the incidence of withdrawal syndrome is in the range 30-60%[58].

Withdrawal syndrome is more likely in the following situations[4,59,60]:

- With antidepressants with a short half-life, such as paroxetine, venlafaxine and desvenlafaxine.
- In patients who do not take the antidepressant regularly and often forget a dose.
- When treatment has persisted for more than 6-8 weeks.
- In patients taking other drugs that act on the central nervous system.
- In patients who develop symptoms of anxiety when starting antidepressant treatment.
- In children and adolescents.
- In patients who have previously experienced withdrawal symptoms.

Treatment should be withdrawn gradually to prevent the onset of withdrawal syndrome

As is the case for all deprescribing, the changes should be successive, therefore in patients taking two or more antidepressants, they should be withdrawn one at a time so that any symptoms which may appear can be attributed to that drug. The patient's age, comorbidities and state, drug interactions, adverse effects and the patient's preferences should all be taken into account when deciding which to deprescribe first[45].

Generally speaking, and except in exceptional cases due to the onset of adverse effects or interactions, the antidepressant should be withdrawn gradually, especially when treatment has been prolonged or in the case of drugs with a short elimination half-life.

The withdrawal syndrome associated with the withdrawal of antidepressants may favour prolonged use thereof as its symptoms can be confused with those of a recurrence of the depressive disorder, thus meaning that the drug is taken long-term with no real need to do so[61]. Moreover, these symptoms may prove to be intolerable for some patients, thereby prolonging treatment without clinical benefit[62].

It is advisable to perform follow-up visits after deprescribing and, in the event that symptoms appear, restart the previous lowest dose, subsequently continuing with deprescribing after 6-12 weeks[63,64].

Deprescribing TCAs[63]

The standard recommendation is to reduce 25-50% of the dose every 1-4 weeks, with slower decreases of 12.5% at the end of the process. Treatment on alternate days should be considered if the dosage forms available are not suitable for the dose required. Treatment is considered to be finalized two weeks after the last dose administered.

Deprescribing SSRIs or SNRIs[64]

Progressive reduction with no change of drug

Reduce the dose by 25-50% every 1-4 weeks. Reduce more slowly at the end of the process. Treatment on alternate days should be considered if the dosage forms available are not suitable for the dose required. Treatment is finalized two weeks after the last dose administered.

The possibility of changing to fluoxetine (long half-life) is available for complex cases: lower probability of withdrawal syndrome

- Convert the SSRI dose to an equivalent dose of fluoxetine in oral solution. For example, 20 mg paroxetine, 75 mg venlafaxine or 20 mg citalopram are equivalent to 20 mg fluoxetine. The oral solution form allows the dose to be reduced more slowly than is possible with solid forms.
- Maintain the fluoxetine dose for 7 days and then reduce by 50%.
- Reductions of 50% per week, or less if problems arise.
- Once a dose of 10 mg fluoxetine has been reached, consider reducing by 1 mg every 2-3 days over a period of several weeks or, if necessary, months.

If problems are encountered during any of these phases, the recommendation is to remain at that stage for a longer period of time before continuing with withdrawal.

It should be remembered that withdrawal symptoms are more common for antidepressants with a short half-life, such as paroxetine, venlafaxine and desvenlafaxine. Indeed, paroxetine should be withdrawn more slowly, over a period of 3-4 weeks.

Fluoxetine, in contrast, has a longer half-life, thus meaning that withdrawal symptoms are less common with this SSRI and, therefore, that it can be withdrawn in 1-2 weeks or even suspended directly.

SWITCHING ANTIDEPRESSANTS

Up to two thirds of patients with major depression do not respond to their first antidepressant treatment. If no improvement is observed after three or four weeks with an appropriate dose of antidepressant, it is recommended to change to another. Approximately one quarter of patients who change to a second antidepressant are expected to achieve remission[65].

Up to two thirds of patients with major depression do not respond to their first antidepressant treatment

It should be noted that there is no evidence that switching between classes of antidepressants is more effective than switching within the same class[66].

In addition to a lack of efficacy, switching antidepressants is also indicated due to the onset of unwanted adverse effects, when new conditions that contraindicate the use of a specific drug appear or when new drugs that interact with the antidepressant are introduced.

The general recommendations issued by the Navarre Health Service as regards the sequence of antidepressant treatment are:

- An SSRI is selected as first choice unless contraindicated.
- Treatment should be maintained for a minimum of 3-4 weeks after optimisation of the dose to determine its success.
- Use of a single drug is associated with a lower risk of adverse effects. As such, if the symptoms do not improve after reaching a sufficient dose of the first drug, the patient should be switched to another antidepressant from the same group rather than adding another drug. In other words, switching to a different SSRI should be considered.
- If two drug treatments from the same therapeutic group (SSRI) have not proved effectiveness, it is recommended to switch to a drug from another group, such as venlafaxine, mirtazapine, mianserin, buproprion or a TCA.

Methods for switching between antidepressants

The entire process should be monitored carefully. Individual patient-related factors and those related to the disease may require modifications to the switching strategy[65]. Different strategies for switching antidepressants are available[57].

Direct switching (Figures 4a, 4b)

The current antidepressant is stopped immediately and the second is started immediately afterwards. This option is useful when treatment started less than 6 weeks previously (lower probability of withdrawal syndrome) or if the switch is due to the onset of serious adverse effects. The advantage of this method is that it is fast and simple. This method may also be indicated when switching between drugs from the same therapeutic group, in other words with the same mechanism of action and at equivalent doses[57].

It is not indicated when we start from fluoxetine (it requires washing period).

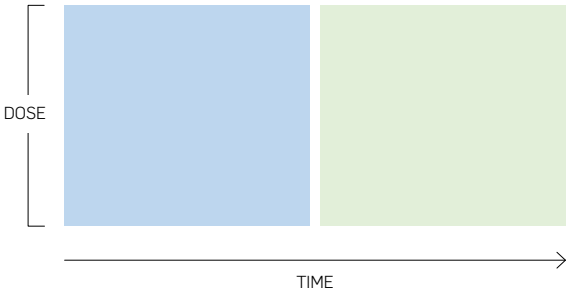

Figure 4a. Direct switch.

A variant of direct switching comprises introducing the second drug immediately after the first, gradually increasing the dose, instead of directly at the full dose. This method is particularly indicated when switching occurs between an SSRI and an SNRI (similar, but not identical, mechanism of action)[67].

Especially indicated in the change from paroxetine to duloxetine or venlafaxine.

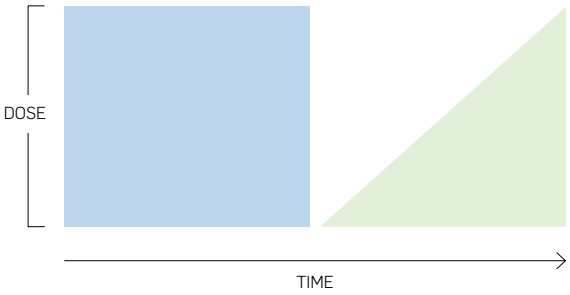

Figure 4b. Gradual direct switch.

Cross-tapering (Figure 4c)

This is the method of choice in most cases. Gradual withdrawal of the first antidepressant and gradual introduction of the second are performed simultaneously and, for a short period of time, both treatments overlap, although not at their full doses. The main drawback is that the concomitant administration of two antidepressants may lead to interactions between them[57].

Especially indicated in patients especially sensitive to withdrawal symptoms, when we start from high doses, when we start with drugs included in the "other" antidepressants group and for switching between SSRIs and TCAs.

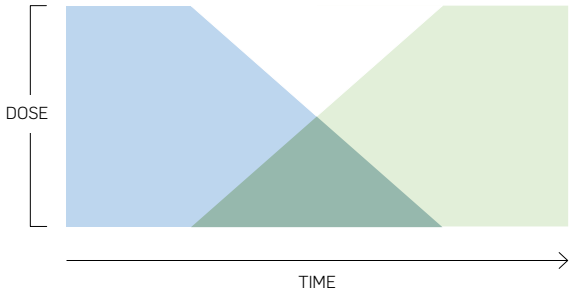

Figure 4c. Cross-tapering.

Overlap switching (Fig 4d)

This is a variant of cross-tapering. The initial antidepressant treatment is maintained while the second antidepressant is introduced gradually until the optimal dose is reached. Once the new drug has been introduced, the initial antidepressant is withdrawn gradually. This strategy may be useful when a partial response has been achieved and the effect obtained needs to be preserved. In this method, the simultaneous administration of both antidepressants, in this case at full doses, increases the probability of adverse effects and interactions[57].

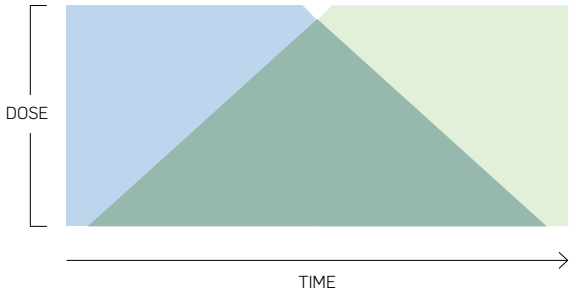

Figure 4d. Overlap switching.

Sequential switching (Figures 4e, 4e)

The first antidepressant is withdrawn gradually and, once withdrawn completely, the second drug is also introduced gradually. Generally speaking, this method is indicated when switching between drugs with potentially significant interactions (MAOI-MAOI). It is a safer, but slower, method. A wash-out period may be introduced between both drugs, with this being particularly suitable when the drug being withdrawn has a long half-life (fluoxetine and MAOI)[57].

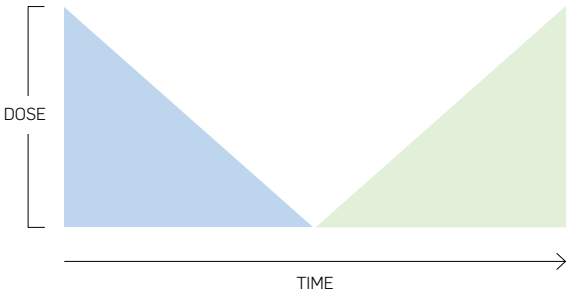

Figure 4e. Sequential switching.

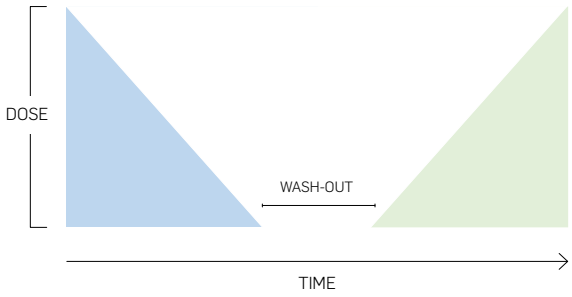

Figure 4f. Sequential switching with wash-out.

Therefore, the most appropriate switching methods depending on the antidepressants involved would be those indicated in table 6.

Table 6. Summary of switching between two antidepressants[57].

	IMAO	TCA	SSRI	SNRI
MAOI	Sequential switching with wash-out of 2 weeks.	Sequential switching with wash-out of 2 weeks.		
TCA	Sequential switching with wash-out of 2 weeks.	Cross-tapering.		
SSRI	Sequential switching with wash-out of 1 week (5-6 weeks for fluoxetine).	Cross-tapering. Sequential switching with wash-out of 1 week (fluoxetine).	Cross-tapering. Sequential switching with wash-out of 1 week (fluoxetine). Direct change to equivalent doses[a].	Cross-tapering. Cambio secuencial con lavado de 1 semana (fluoxetina). Direct change with caution[b].
SNRI	Sequential switching with wash-out of 1-2 weeks.	Cross-tapering.	Cross-tapering. Direct change with caution[b].	Cross-tapering. Direct change to equivalent doses.

(a) Except when starting from fluoxetine. (b) Especially for paroxetine to duloxetine or venlafaxine.
TCA: Tricyclic antidepressant; SSRI: Selective serotonin reuptake inhibitor.

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ANNEXED

EVALUATING DEPRESSION

Routine screening for depression is not recommended in the general population given the doubts surrounding its effectiveness[1].

A clinical interview is an essential tool for diagnosing depression[2].

It is recommended to remain alert for the possibility of depression, especially in patients with risk factors and who also present symptoms such as insomnia, low mood and suicidal ideation. Whenever a sign of depression is noted in a routine primary care examination, the use of two questions (Whooley questions) concerning mood and the ability to enjoy is recommended to evaluate the possible presence of a depressive condition:

- During the past month: have you often been bothered by feeling down, depressed or hopeless?
- During the past month: have you often been bothered by little interest or pleasure in doing things?

If the patient answers "yes" to either of these questions, an appropriate psychopathological assessment should be performed[1].

When evaluating depression, both ICD-10 and DSM-IV provide a series of consensual criteria that can be used (tables 1 and 2), although an assessment of depression should be carried out with a broad-ranging focus and should not be based solely on the number of symptoms as several different factors may affect the development, progression and severity of depression. Some of the areas to be assessed are as follows[2]:

- Characteristics of the episode: duration, number and intensity of the symptoms, comorbidity.
- Psychosocial assessment (social support and interpersonal relationships).
- Associated degree of dysfunction and/or disability.
- Previous response to treatment.
- Suicide risk.

Different scales are used to evaluate the severity of depression and its response to treatment. Although they are not used systematically in clinical practice, there is a consensus regarding the need to incorporate such scales into clinical practice, especially for monitoring response to treatment and the evolution of the depression[3].

The scales validated for assessing depression include:

Table 1. Symptoms of major depression. DSM-IV diagnostic criteria[2].

1	Depressed mood
2	Diminished interest or pleasure
3	Changes in weight or appetite
4	Sleep abnormalities
5	Psychomotor activity alterations
6	Lack of energy
7	Feelings of worthlessness or guilt
8	Diminished ability to think or concentrate, or make decisions
9	Recurrent thoughts of death or suicidal ideation

» At least five symptoms (from those in the first column) over a period of at least two weeks that represent a change with respect to previous activity.

» At least one of them must be depressed mood or diminished interest or pleasure.

» These symptoms must interfere with daily living.

» Not drug-related.

» No history of manic or hypomanic episodes.

Table 2. General diagnostic criteria for a depressive episode as per ICD-10[2].

A	The depressive episode must last for at least two weeks.
B	The episode cannot be attributed to abuse of psychoactive substances or an organic mental disorder.
C	Somatic syndrome: "somatic" symptoms are commonly considered to have a special clinical significance and are referred to as "melancholic" or "endogenomorphous" in other classifications. • Marked loss of interest or ability to enjoy activities that would normally be pleasurable. • Absence of emotional reactions to events that normally provoke a response. • Waking up in the morning two or more hours before the normal time. • Worsening of depressive mood in the morning. • Agitation or slowing of movement. • Marked loss of appetite. • Weight loss of at least 5% in the past month. • Marked decrease in sexual interest.

- Beck Depression Inventory (BDI-II).
- Hamilton Rating Scale for Depression (HRDS).
- Montgomery Asberg Depression Rating Scale (MADRS).
- Brief Patient Health Questionnaire (PHQ-9).

Both the original and subsequent versions of these scales have been adapted to, and validated in, Spanish.

BDI-II

One of the most widely used. The objective is to detect the presence of depressive symptoms and quantify their severity. It comprises 21 items, and for each of them, the patient must choose the phrase that best describes their state during the past two weeks from amongst four alternatives ordered from lesser to greater severity. Each item is given a score of between 0 and 3 points, depending on the alternative selected and, after summing all the scores, a total score of between 0 and 63 is obtained.

The cut-off points are as follows: No depression (0-9); mild depression (10-16); moderate depression (17-29); severe depression (>30).

Hamilton Test (HRDS)

This is one of the most widely used to monitor the evolution of depressive symptoms. Upon summing the scores for each item, the Hamilton scale provides a global score for the severity of the depressive symptoms.

The cut-off points are as follows: No depression (0-7); sub-clinical depression (8-13); mild depression (14-18); moderate depression (19-22) and severe depression (>23).

Response to treatment is typically defined as a decrease of 50% or more of the initial score, partial response as a decrease of 25–49%, and no response as a decrease of less than 25%. Remission is considered to have been achieved at a score of ≤7.

MADRS

This scale comprises 10 items to assess the severity of depressive symptoms. The score for each item ranges between 0 and 6 points, and the clinical may use sources of information other than the patient to assign the score. Compared with Hamilton, it has the advantage of not being contaminated by items evaluating anxiety. The global score is obtained by summing the score assigned to each item, and ranges between 0 and 60.

The cut-off points are as follows: No depression (0-6); mild (7-19); moderate (20-34) and severe (35-60).

As for the Hamilton scale, response to treatment is defined as a decrease of 50% or more of the initial score, partial response as a decrease of 25–49%, and no response as a decrease of less than 25%. Remission is considered to have been achieved at a score of ≤10.

PHQ-9

This comprises nine items that evaluate the presence of depressive symptoms (corresponding to the DSM-IV criteria) present in the past two weeks. A diagnosis of major depression is suggested when five of the nine symptoms have been present "for more than half the days" in the past two weeks and one of the symptoms is mood-related. The overall score ranges from 0 to 27 and each item is scored on a scale of 0 (never) to 3 (more than half of the days). Moreover, this scale includes an additional question to gain a better understanding of the degree of interference of the symptoms with daily living.

The cut-off points are as follows: Minimal or mild depressive symptoms (<10); mild depression (10-14); moderate (15-19) and severe (20-27).

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