Chapter 10

Use of Antidepressants in Children and Adolescents

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Additional information is available at the end of the chapter

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Abstract

Depression is a serious disorder that can cause significant problems in mood, thinking, and behavior at home, in school, and with peers. It is estimated that major depressive disorder (MDD) affects about 5% of adolescents. Research has shown that, as in adults, depression in children and adolescents is treatable. Certain antidepressant medications, called selective serotonin reuptake inhibitors (SSRIs), can be beneficial to children and adolescents with MDD. Certain types of psychological therapies also have been shown to be effective. However, our knowledge of antidepressant treatments in youth, though growing substantially, is limited compared to what we know about treating depression in adults. The U.S. Food and Drug Administration (FDA) issued a public warning in October 2004 about an increased risk of suicidal thoughts or behavior (suicidality) in children and adolescents treated with SSRI antidepressant medications. However, SSRI medications are considered to have an improvement over older antidepressant medications and they have been shown to be safe and effective for adults. In this chapter we provide an updated and well-documented review of the current scientific evidence on this topic.

Keywords: antidepressants, children, adolescents

1. Overview

Major depressive disorder (MDD) is one of the most common mental disorders in children and adolescents [1, 2]. Although the estimated prevalence is 5–6% in adolescents aged 13–18 years and 5–6% in children aged 6–12 years, there are fewer studies to understand how antidepressants work in this age group [1]. Children and adolescents present with undifferentiated depressive symptoms, like irritability, school refusal, and aggressive behavior [3], which is

possible the main reason why major depressive disorder is still under diagnosed and untreated comparing to adults. Depression often impaired social functioning and it may cause suicidal ideation and attempts as a symptom of low mood [4]. Use of antidepressants is wide, in spite of the recommendations of psychotherapy as first-line treatment in most clinical trials [5]. In 2004, the US Food and Drug Administration (FDA) practitioners set a black-box warning relating the use of antidepressants in children and adolescents to an increased risk of suicide [7]. Since then, the use of antidepressants in this group of age remains controversial [3].

The European Medicines Agency has completed its review of two classes of antidepressants and concluded that they should not be used in children and adolescents except in their approved indications [4, 6]. The review of serotonin-selective reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) medicines looked at the potential risk of suicidal behavior in children and adolescents treated with these products [13].

The Agency's scientific committee, the Committee for Medicinal Products for Human Use (CHMP), concluded at its April 19–22, 2005 meeting that suicide-related behavior (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behavior, and anger) were more frequently observed in clinical trials among children and adolescents treated with these antidepressants compared to those treated with placebo [13].

The Agency's committee is therefore recommending the inclusion of strong warnings across the whole of the European Union to doctors and parents about these risks. Doctors and parents will also be advised that these products should not be used in children and adolescents except in their approved indications [13].

Most of these products are approved for the treatment of depression and anxiety in adults in the European Union, but are not licensed Europe-wide for the treatment of these conditions in children or adolescents. Some of these products are however licensed for pediatric use for the treatment of obsessive-compulsive disorder and one of them for the treatment of attention deficit/hyperactivity disorder [13].

The efficacy of antidepressants is well documented among adults with major depressive disorder, however, in children and adolescents there are fewer studies and they tend to have worse methodology and more risk of bias [8, 9]. Randomized controlled trials (RCT) have shown that antidepressants agents have positive risk-benefit ratio in children and adolescents, but their clinical use should balance the potential risk and the clinical need. Young people should be closely monitored for suicidal ideation and behaviors, especially when starting an antidepressant and at dosage adjustments [7].

A recent network meta-analysis has proved antidepressants to be well-tolerated in major depressive disorder in children and adolescents [9], although they do not seem to offer a clear advantage against psychotherapeutic interventions. These trials include use of amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine [8]. Only fluoxetine showed statistically significant differences with placebo. In terms of tolerability, fluoxetine was better than duloxetine and imipramine. According to these results, fluoxetine should be considered the best option when considering medication to treat moderate-to-severe depression in children and adolescents, when they do not have access to psychotherapy or have not responded

to nonpharmacological interventions. Evidence suggests a significantly increased risk for suicidality (suicidal behavior or ideation) in young people given venlafaxine for the treatment of major depressive disorder [10].

2. Selective serotonin reuptake inhibitors (SSRIs)

2.1. Fluoxetine

2.1.1. Pharmacodynamics

- Action mechanism: fluoxetine increases the release of serotonin (5-HT) and inhibits reuptake pump. Possibly increases serotonergic neurotransmission.
- A receptor affinity: receptors desensitize 5-HT, especially 5-HT1A autoreceptors. It also has antagonist properties on 5-HT2C (serotonin) receptors, which could increase the release of norepinephrine and dopamine.

2.1.2. Pharmacokinetics

Fluoxetine is absorbed in gastrointestinal tract and metabolized by the liver. The active metabolite, norfluoxetine, has a half-life of 2 weeks. The original drug has a half-life of 2–3 days. Inhibits cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A (CYP3A).

2.1.3. Drug and food interactions

- Fluoxetine can increase tricyclic antidepressants concentrations.
- It can cause a fatal serotonin syndrome when combined with monoamine oxidase inhibitors (MAOIs), so it should be used only after 14 days of treatment with this group of drugs.
- It can displace other drugs with high protein binding (warfarin).
- It can cause weakness, hyperreflexia, and incoordination when combined with sumatriptan and other triptans.
- It can cause bleeding, especially when combined with other blood thinners.
- It may interfere with the analgesic actions of codeine (by inhibiting CYP2D6). By the same route could increase the concentration of atomoxetine and some beta-blockers. It could increase concentrations of thioridazine and cause heart arrhythmias.
- It can reduce the clearance of trazodone and diazepam, increasing their concentrations.
- By inhibiting cytochrome CYP3A4 may increase concentrations of alprazolam, buspirone, and triazolam as well as the concentration of some cholesterol-lowering HMG Coa (3-hidroxi-3-metilglutaril-coenzima A o β-hidroxi-β-metilglutaril-coenzima A) (e.g., simvastatin, atorvastatin, and lovastatin).

- It could increase concentrations of pimozide and produce dangerous QTc prolongation and cardiac arrhythmias.
- Tramadol increases the convulsion risk in patients taking antidepressants.

2.1.4. Side effects and toxicology

- Sexual dysfunction.
- Decreased appetite, nausea, diarrhea, constipation, and dry mouth.
- Insomnia, sedation, agitation, tremors, headache, and dizziness.
- Sweating.
- Hematomas and rarely bleeds.
- Patients diagnosed with bipolar disorder, psychotic disorder, or bipolar or psychotic disorder undiagnosed may be more vulnerable to the pharmacological actions of SSRIs on the central nervous system (CNS).

The appearance of these side effects by itself does not need the withdrawal of the drug, but the decision should be individualized. Sometimes these adverse effects could be very disturbing por the patient, so if this happens we recommend to decrease the dose and wait, being able to rise again progressively in case of improving the symptoms. In case of persistent effects despite decreasing the dose, consider withdrawing the drug.

In high risk bleeding patients, consider prescribing another antidepressants (nonSSRIs). In patients taking antidepressants with high affinity for serotonin receptors, it is advised to avoid or decrease the use of nonsteroidal anti-inflammatory drugs or aspirin.

2.1.5. Use in children and adolescents

- Posology: fluoxetine has been approved for depression and obsessive-compulsive disorder (OCD). Teens usually receive the same dose as adults, children receive slightly lower dose. They should be administered in a single dose, usually in the morning. The liquid solution facilitates management in children.
- How to start treatment: you have to gradually increase the drug. The starting dose is 10 mg/day for anxiety disorders and depressive disorders; gradually increase the dose to achieve therapeutic range (usually 20 mg/day). In bulimia nervosa, the dose is 60–80 mg/day in adolescents and in children slightly lower.
- Phase maintenance dose should be carefully adjusted: it is recommended that treatment should be maintained between 6–12 months after reaching the clinical improvement.
- For long-term use: it is safe for an extended period.
- Treatment withdrawal: no need to taper the dosage as fluoxetine alone is removed gradually due to the long half-life that has and shares with its active metabolites.

2.2. Sertraline

2.2.1. Pharmacodynamics

- Action mechanism: potentiates the action of 5-HT by blocking the reuptake pump. Increases 5-HT neurotransmission.
- Pharmacological profile: has an affinity for the receptors. Desensitizes especially 5HT-1A. It has slight antagonistic actions in the sigma receptors.

2.2.2. Pharmacokinetics

The original drug has a half-life of 22–36 hours. The half-life of the metabolite is from 62 to 104 hours. Also, inhibits CYP2D6 and CYP3A4 (weakly).

2.2.3. Drug and food interactions

- Sertraline may increase concentrations of tricyclic antidepressants (TCA).
- It can cause a fatal serotonin syndrome when combined with MAOIs.
- It can displace protein-based drugs (e.g., warfarin).
- It can increase the risk of bleeding when combined with anticoagulant.
- It can produce boxes infrequently weakness, hyperreflexia, and incoordination when combined with sumatriptan and other triptans, requiring close monitoring of the patient.
- By inhibition of CYP2D6 could interfere with the analgesic action of codeine, increasing concentrations of thioridazine, and cause dangerous cardiac arrhythmias.
- By inhibiting CYP3A4 could increase the concentrations of alprazolam, buspirone, and triazolam, and the concentrations of certain hypolipidemic inhibitors HMG CoA reduced (particularly simvastatin, atorvastatin, and lovastatin).
- It could increase concentrations of pimozide and prolong the QTc interval and dangerous cardiac arrhythmias.
- Tramadol increases the convulsion risk in patients taking antidepressants.

2.2.4. Side effects and toxicology

- Sexual dysfunction.
- Gastrointestinal: nausea, decreased appetite, diarrhea, constipation, dry mouth.
- CNS: insomnia or sedation, agitation, tremor, headache, and dizziness.
- Autonomic: sweating.
- Haemorrhaging is rare.

- Hyponatremia is rare.
- Hypotension is rare.

As we discuss with fluoxetine, the appearance of these adverse effects alone does not need withdrawal of the drug, but the decision should be individualized. If these adverse effects are very annoying to the child, we recommend decreasing the dose and wait, being able to rise again progressively in case of improving the side effects. In case of persistent effects despite decreasing the dose, consider withdrawing the drug.

Note: Patients with diagnosed or bipolar disorder or psychotic disorders may be more vulnerable to the pharmacological actions of SSRIs.

Toxicology: It is rare to be lethal in overdose alone; vomiting, sedation, abnormal heart rhythm, mydriasis, agitation; deaths have been reported with overdoses of sertraline, in combination with other drugs or alcohol.

2.2.5. Use in children and adolescents

- Posology: for children aged 6–12 years, the initial dose is 25 mg/day. From the age of 13, one can start the adult dose of 50 mg daily.
- How to start treatment: gradual increase in dose, 25 mg/7 days to reach the minimum effective dose.
- Maintenance phase: the dose should be carefully adjusted and maintain the drug for 6–12 months after clinical improvement.
- Long-term use: it is safe for an extended period.
- Treatment withdrawal: the dose should be gradually reduced to avoid withdrawal symptoms (dizziness, nausea, stomach cramps, sweating, tingling, and dysesthesia). Some patients tolerate a decrease of 50% of the dose in 3 days, another 50% over the next 3 days to complete withdrawal.

2.3. Citalopram

2.3.1. Pharmacodynamics

- Action mechanism: blocking reuptake pump 5-HT, serotonin neurotransmission increasing.
- Pharmacological profile: receptor affinity. Increases concentration of 5-HT receptors and desensitizes, especially, 5-HT1A.

2.3.2. Pharmacokinetics

The original drug has a half-life of 23–45 hours. It is a weak inhibitor of CYP2D6.

2.3.3. Drug and food interactions

- Citalopram can increase tricyclic antidepressants concentrations.
- It can cause a fatal "serotonin syndrome" when combined with MAOIs. One should not start treatment with citalopram at least until two weeks after stopping the MAOI.
- It can displace drugs with strong protein (e.g., warfarin) union.
- Once can cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or other triptans, requiring careful monitoring of the patient.
- Possibly increases the risk of bleeding when combined with anticoagulant.
- By inhibition of CYP2D6 pathway could interfere with codeine analgesic and increases plasma concentrations of some beta-blockers and atomoxetine.
- By the same route could increase concentrations of thioridazine and causes dangerous cardiac arrhythmias.

2.3.4. Side effects

- Sexual dysfunction.
- Gastrointestinal: decreased appetite, nausea, diarrhea, constipation, and dry mouth.
- On CNS: insomnia, sedation, agitation, tremors, headache, and dizziness.
- Autonomic: sweating.
- Hematomas and bleeding (rare).
- Hyponatremia (rare).
- Syndrome of inappropriate secretion antidiuretic hormone (SIADH).

The advice for action in case of appearance of side effects is the same as that discussed in previous SSRIs.

2.3.5. Toxicology

- Citalopram overdose death can occur rarely.
- Can cause vomiting, sedation, heart rhythm disturbances, dizziness, sweating, nausea, and trembling.
- Rarely produces amnesia, confusion, coma, and convulsions.

2.3.6. Use in children and adolescents

- Posology: the right dose in children is 5–10 mg/day. In adolescents it may be administered to 10–20 mg/day.
- Phase maintenance: carefully adjust the dose. You can increase the dose to 5 mg/day after one or two weeks. In adolescents it can be increased to 10 mg/day after one or more weeks until the desired effectiveness. The maximum is 60 mg/day. It can be administered as a single dose in the morning or evening.
- For long-term use: it is safe for an extended period.
- Treatment withdrawal: no progressive reduction of the drug is needed. However, it is advisable to avoid potential withdrawal symptoms. Most patients tolerate doses decreased 50% in 3 days; another 50% reduction in 3 days, and then the dose may be suspended. If withdrawal symptoms appear during reduction, the dose should be increased to stop symptoms. Restart the reduction more progressively.

2.4. Escitalopram

2.4.1. Pharmacodynamics

- Action mechanism: enhanced release of 5-HT reuptake inhibiting pump.
- Pharmacological profile: receptor affinity. Desensitize 5-HT receptors, especially 1A autoreceptors.

2.4.2. Pharmacokinetics

The elimination half-life is 27–36 hours. Stable mean plasma concentrations are reached within weeks. It has no effect on the CYP450.

2.4.3. Drug and food interactions

- Tramadol increases the risk of convulsion in patients taking antidepressants.
- Can cause a fatal "serotonin syndrome" when combined with MAOIs; not starting an MAOI up to 14 days after it is suspended.
- It could theoretically cause weakness, incoordination hyperreflexia, and when combined with sumatriptan or other triptans, so careful monitoring of the patient is necessary.
- It can increase the risk of bleeding, especially when combined with anticoagulants.

2.4.4. Side effects

- Sexual dysfunction.
- Gastrointestinal (decreased appetite, nausea, diarrhea, constipation, and dry mouth).

- On CNS (insomnia, sedation, agitation, tremors, headache, and dizziness).
- Autonomic (Sweating).
- Hematomas and bleeding (rare).
- Hyponatremia (rare).

The advice for action in case of appearance of side effects is the same as that discussed in previous SSRIs.

2.4.5. Toxicology

Mortality is rare to the overdose of escitalopram alone or in combination with other drugs. Symptoms associated with overdose are nausea, vomiting, sedation, sweating, tremor, and rarely amnesia, coma, and convulsions.

2.4.6. Use in children and adolescents

- Dosage: recommended for children 5–10 mg/day and for adolescents 10–15 mg/day.
- Home treatment: gradual dose escalation. In children, we must start at a dose of 5 mg/day, reaching up to 10 mg/day. In adolescents, we will start with a dose of 10 mg/day, increasing the dose to 15–20 mg/day.
- Maintenance phase: the dose should be carefully adjusted. Maintaining treatment is recommended 6–12 months produced clinical improvement.
- Long-term use: it is safe for an extended period.
- Treatment withdrawal: no need to make a gradual decline but it is wise to carry it out to avoid a withdrawal syndrome. Many patients tolerate a decrease of 50% of the dose in 3 days, and then the other 50%. If withdrawal symptoms appear during the gradual decline of the drug, the dose can be increased until they disappear. Restart the reduction more progressively.

There are other antidepressants such as paroxetine and fluvoxamine that have not demonstrated superior efficacy to placebo in children and adolescents with depression.

3. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Although none of them is approved by European Medicines Agency or US FDA, some antidepressants not related with SSRI have also been used to children and adolescents for childhood and juvenile depression and anxiety disorders.

3.1. Venlafaxine

3.1.1. Pharmacodynamics

Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). Although, the exact mechanism of action is not well known, venlafaxine and its metabolite,

O-desmethylvenlafaxine (ODV) inhibit the reuptake of serotonin at low doses, serotonin and norepinephrine (NE) at higher doses, and have a weak inhibitory effect on the reuptake of dopamine at even higher doses. Venlafaxine has little affinity for histaminergic, cholinergic, and alpha-adrenergic receptors, not clinically significant.

3.1.2. Pharmacokinetics

Venlafaxine is well absorbed. Food does not affect the absorption of venlafaxine. Bioavailability is 45% following oral administration. Venlafaxine is metabolized by cytochrome P450 2D6 and cytochrome P450 2C19 to ODV, the major metabolite, which is clinically active. Renal elimination is the main route of excretion. The half-life is about 5–11 hours.

3.1.3. Drug and food interactions

Venlafaxine is a moderate inhibitor of cytochrome P450 2D6. Tramadol increases the risk of seizures in patients taking antidepressants. Venlafaxine could inhibit the metabolism of tramadol, reducing his analgesic efficacy and increasing the risk of serotonin syndrome.

3.1.4. Side effects and toxicology

- Sustained elevation of blood pressure is dose-dependent (rarely occurs below 255 mg/day doses) related to inhibition of NE reuptake. In patients with sustained blood pressure raises during venlafaxine therapy, dose reduction, or discontinuation should be considered. Monitoring blood pressure and heart rate is recommended when using venlafaxine.
- Sexual dysfunction, especially abnormal ejaculation and orgasm.
- Gastrointestinal: nausea, dry mouth, constipation. Consider reducing the dose if these symptoms are annoying.
- Central nervous system: sedation, dizziness, nervousness, anxiety, insomnia, somnolence, and tremor. Consider reducing the dose if these symptoms are annoying.
- Mydriasis: patients at risk of angle-closure glaucoma should be monitored.
- In young people, venlafaxine could lead to decrease appetite and weight loss.
- While all antidepressants have the black-box warning about increased suicidal behaviors, venlafaxine is the only one that have demonstrated in RCT and meta-analysis to be associated with higher rates of self-harm events in patients with higher levels of suicidal thoughts. Close monitoring of suicidal ideation and behaviors is necessary during treatment with this drug.

3.1.5. Use in children and adolescents

Venlafaxine is FDA approved for major anti-inflammatory in adults; meanwhile extended-release venlafaxine is approved for the treatment of adults with generalized anxiety disorder, panic disorder, and social phobia besides major depressive disorder.

Two multicenter, randomized, double-blind, and placebo-controlled trials have evaluated the efficacy and tolerability of venlafaxine extended release (ER) for children and adolescents with major depressive disorder. The primary main outcome was the Children's Depression Rating Scale-Revised (CDRS-R) total score. Analysis of each trial independently showed no statically significance between venlafaxine ER and placebo. In the age subgroup analysis, the pooled data showed greater improvement with venlafaxine ER among adolescents (ages 12–17) but not among children (ages 7–11). This study also found that hostility and suicide-related events were more common in venlafaxine ER-treated participants than in placebo-treated participants. There were no completed suicides.

The treatment of resistant depression in adolescents (TORDIA) study was a RCT of treatment resistant adolescents (ages 12–18) with major depressive disorder, who had not responded to a 2-month treatment with an SSRI. Then they were randomized to another SSRI alone, alternate SSRI plus cognitive behavioral therapy (CBT), venlafaxine alone, or venlafaxine plus CBT. Combination of CBT and a switch to another antidepressant had a higher rate of clinical response than medication alone. Changing to an alternate SSRI or venlafaxine had no different response rates. Venlafaxine groups have shown increase in blood pressure and frequency rate, rarely of clinical impact.

Venlafaxine ER has been also studied for anxiety disorders. An RCT of 320 youth (ages 6–17) diagnosed with generalized anxiety disorder shown statistically significant improvement in both the primary outcome and the response rate compared to placebo. Statistically significant changes in weight, blood pressure, pulse, and cholesterol levels were observed in the venlafaxine ER group.

3.1.6. Dosage and administration in children and adolescents

- Venlafaxine dosing schedule among children is similar to adults.
- Home treatment: the recommended initial dosage is 37.5 or 75 mg daily administered in 2 or 3 doses or as a single dose daily when using extended-release capsules. To minimize nausea and other gastrointestinal symptoms, venlafaxine should be taken with food.
- Maintenance phase: the dosage can be increased by 75 mg daily every 4–7 days. A total of 225 mg daily is the maximum dose recommended. Maintaining treatment is recommended 6–12 months produced clinical improvement.
- Long-term use: it is safe for an extended period.
- Treatment withdrawal: no need to make a gradual decline but it is wise to carry out to avoid a withdrawal syndrome. We advise to a decrease of 37.5 mg every 6 days. If withdrawal symptoms appear during the gradual decline of the drug, the dose should be increased until they disappear and then start the reduction again.

3.2. Desvenlafaxine

3.2.1. Pharmacodynamics

Desvenlafaxine (O-desmethylvenlafaxine), the major metabolite of venlafaxine, is a selective serotonin and norepinephrine reuptake inhibitor. As venlafaxine and desvenlafaxine inhibit

the reuptake of serotonin at low doses, serotonin and norepinephrine at higher doses, and have a weak inhibitory effect on the reuptake of dopamine at even greater doses. Desvenlafaxine has no clinically significant affinity for histaminergic, cholinergic and alpha-adrenergic receptors.

3.2.2. Pharmacokinetics

Bioavailability is approximately 80% and is unaffected by food. Desvenlafaxine undergoes simple metabolism via conjugation mediated by UGT isoforms and oxidative N-demethylation via cytochrome P450 3A4 to a minor extent. CYP2D6 is not involved. Approximately 45% of the total oral dose is excreted by urine as unchanged desvenlafaxine. The half-life is about 11 hours.

3.2.3. Drug and food interactions

Compared to other SSNRIs, desvenlafaxine has a low risk of drug-drug interactions since there is minimal metabolization by cytochrome P450 pathway.

3.2.4. Side effects and toxicology

- Sustained elevation of blood pressure, dose-dependent, related to inhibition of NE reuptake. Monitoring blood pressure and heart rate is recommended when using desvenlafaxine. In patients with sustained blood pressure raises during desvenlafaxine therapy, dose reduction or discontinuation should be considered.
- Sexual dysfunction, especially abnormal ejaculation and orgasm.
- Gastrointestinal: nausea, dry mouth, constipation.
- Central nervous system: sedation, dizziness, nervousness, anxiety, insomnia, somnolence, and tremor.
- Mydriasis: patients at risk of angle-closure glaucoma should be monitored.

3.2.5. Use in children and adolescents

Desvenlafaxine is FDA approved for the treatment of major depressive disorder in adults. There is no clinical study in the literature about the use of desvenlafaxine in the pediatric population.

3.2.6. Dosage and administration in children and adolescents

- Desvenlafaxine is presented in 50 and 100 mg extended-release tablets.
- Home treatment: the recommended initial dosage is 50 mg as a single dose daily.
- Maintenance phase: the dosage can be increased by 50 mg daily every 4–7 days. Clinical studies have not observed additional efficacy with dosages greater than 50 mg but side effects were more common. A total of 200 mg daily is the maximum dose recommended. Maintaining treatment is recommended 6–12 months produced clinical improvement.

- Long-term use: it is safe for an extended period.
- Treatment withdrawal: the dosage should be decreased gradually to prevent withdrawal symptoms like dizziness, gastrointestinal discomfort, headache, nervousness, or agitation. Many patients tolerate a decrease of 50% of the dose in 3–7 days and then the other 50%. If withdrawal symptoms appear during the gradual decline of the drug, the dose should be increased until they disappear and then start the reduction again.

3.3. Duloxetine

3.3.1. Pharmacodynamics

Duloxetine is another selective serotonin and norepinephrine reuptake inhibitor (SSNRIs). The major difference to venlafaxine is that duloxetine has comparable binding affinity to both norepinephrine and serotonin transport sites. Duloxetine has no significant affinity for dopaminergic, histaminergic, cholinergic, and alpha-adrenergic receptors.

3.3.2. Pharmacokinetics

Duloxetine is well absorbed and unaffected by food. Protein binding is greater than 90%. Duloxetine is metabolized by cytochrome P450 2D6 and 1A2 to the metabolites, which are not active. Renal elimination is the main route of excretion (70%) followed by fecal excretion (20%). The half-life is about 12 hours [8–17].

3.3.3. Drug and food interactions

Duloxetine is a moderate inhibitor of cytochrome P450 2D6. Tramadol increases the risk of seizures in patients taking antidepressants. As result of a pharmacokinetic interaction, duloxetine could increase plasma levels of thioridazine, which may result in increased risk of ventricular arrhythmias.

3.3.4. Side effects and toxicology

- Increase of heart frequency, dose-dependent. Monitoring blood pressure and heart rate is recommended when using duloxetine. In patients with sustained effects, dose reduction or discontinuation should be considered.
- Sexual dysfunction especially decreased sexual desire and problems with erection.
- Gastrointestinal: nausea, dry mouth, constipation, decreased appetite.
- Central nervous system: fatigue, sedation, dizziness, somnolence.

3.3.5. Use in children and adolescents

Among adults, duloxetine is usually used for the acute and maintained treatment of major depressive disorder, acute treatment of anxiety disorders, fibromyalgia, and neuropathic pain, especially when is associated with peripheral neuropathy.

Two multicenter, randomized, double-blind, and placebo-controlled trials have evaluated the efficacy and safety of duloxetine for children and adolescents with major depressive disorder and compared to fluoxetine. The primary main outcome was the Children's Depression Rating Scale-Revised (CDRS-R) total score. In these studies, neither duloxetine nor fluoxetine demonstrated a statistically significant improvement compared with placebo. Headache and nausea were the main treatment-emergent adverse events. Weight decrease was more common among duloxetine and fluoxetine groups compared to placebo. Suicidal behavior did not occur in acute treatment, while seven cases occurred during extended treatment. There were no completed suicides. No patients had sustained elevation in systolic or diastolic blood pressure during the 36-week study.

Another randomized, double-blind, and placebo-controlled trials have evaluated duloxetine for children and adolescents with generalized anxiety disorder. They found that duloxetine was statistically better than placebo on Pediatric Anxiety Rating Scale (PARS).

3.3.6. Dosage and administration in children and adolescents

- Duloxetine is presented in 20, 30, and 60 mg capsules.
- Home treatment: the recommended initial dosage is 30 mg as a single dose daily in the morning.
- Maintenance phase: the target dose is 30–60 mg in both adolescents and children. Clinical studies have not observed additional efficacy with dosages greater than 60 mg but side effects were more common. A total of 120 mg once a day is the maximum dose recommended. Maintaining treatment is recommended 6–12 months produced clinical improvement.
- Long-term use: it is safe for an extended period.
- Treatment withdrawal: the dosage should be gradually decreased over at least 2 weeks to prevent withdrawal symptoms like gastrointestinal discomfort, headache, nervousness, or agitation. If withdrawal symptoms appear during the gradual decline of the drug, the dose should be increased until they disappear and then start the reduction again.

4. NaSSRI

4.1. Mirtazapine

4.1.1. Pharmacodynamics

Mirtazapine is a piperazinoazepine with an anxiolytic effect. Mirtazapine acts as an antagonist at central presynaptic alpha-2-receptors. This antagonism inhibits negative feedback to the presynaptic nerve and enhances the release of both norepinephrine and serotonin. Mirtazapine is also a weak antagonist of 5-HT1 receptors and a potent antagonist of 5-HT2 (particularly subtypes 2A and 2C) and 5-HT3 receptors. Mirtazapine could also cause sedation through H1

receptor antagonism. It has minimal activity at dopaminergic and muscarinic receptors and NE and 5-HT reuptake are not affected.

4.1.2. Pharmacokinetics

Mirtazapine is completely absorbed but, due to first-pass metabolism, bioavailability is about 50%. Protein binding is about 85%. Duloxetine is metabolized by cytochrome P450 3A4, 2D6 and to a lesser extent by 1A2 to many different metabolites, several of whom are active, but plasma levels are low. Kidneys excrete about 75% of mirtazapine. Half-life is about 20–40 hours.

4.1.3. Drug and food interactions

Mirtazapine is a weak CYP2D6 inhibitor. CYP3A4 potent inhibitors could increase plasma levels of mirtazapine. Adding another serotonin antidepressant may produce serotonin syndrome

4.1.4. Side effects and toxicology

- Mirtazapine is usually well-tolerated.
- The most common adverse effects are sedation and weight gain due to increased appetite.
- Gastrointestinal: dry mouth, constipation.
- Central nervous system: dizziness.

4.1.5. Use in children and adolescents

Mirtazapine is an FDA approved for the acute and maintenance treatment of major depressive disorder in adults.

Few studies till date have evaluated mirtazapine in children and adolescents. There is not strong data with double-blind and placebo-controlled trials. In a recent network meta-analysis, Cipriani and colleagues reported two randomized, placebo-controlled trials funded by a pharmaceutical company in 170 patients aged 7–17. Mirtazapine was not significantly different to placebo on any outcome rating.

4.1.6. Dosage and administration in children and adolescents

- Mirtazapine is available in 15, 30, and 45 mg tablets.
- Home treatment: the recommended initial dosage is 15 mg as a single dose daily at night before bedtime, due to its sedative effects.
- Maintenance phase: the target dose is 30–45 mg in both adolescents and children. 45 mg daily is the maximum dose recommended.

- Long-term use: it is safe for an extended period.
- Treatment withdrawal: the dosage should be gradually decreased over at least 2 weeks to prevent withdrawal symptoms like gastrointestinal discomfort, headache, nervousness, or agitation. If withdrawal symptoms appear during the gradual decline of the drug, the dose should be increased until they disappear and then start the reduction again.

5. MAOI

5.1. Nonselective

5.1.1. Tranylcypromine

5.1.1.1. Pharmacodynamics

5.1.1.1.1. Action mechanism

Tranylcypromine irreversibly blocks monoamine oxidase (MAO) from breaking norepinephrine, serotonin, and dopamine. This presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission. As the drug is structurally related to amphetaine, it may have some stimulant-like actions due to monoamine release and reuptake inhibition [14].

5.1.1.1.2. Pharmacological profile

Tranylcypromine is a nonhydrazine monoamine oxidase inhibitor with a rapid onset of activity. It increases the concentration of epinephrine, norepinephrine, and serotonin in storage sites throughout the nervous system and, in theory, this increased concentration of monoamines in the brain stem is the basis for its antidepressant activity [14].

5.1.1.1.3. Pharmacokinetics

Tranylcypromine achieves an initial peak within approximately 1 hour and a secondary peak within 2–3 hours. It has been suggested that this apparent biphasic absorption in some individuals may represent different absorption rates. Following discontinuance of tranylcypromine, the drug is excreted within 24 hours. On withdrawal of tranylcypromine, MAO activity is recovered in 3–5 days (possibly in up to 10 days). Concentration of urinary tryptamine, an indicator of MAO-A inhibition return to normal, however, within 72–120 hours [14].

5.2. Selective

5.2.1. Moclobemide

Moclobemide is a reversible inhibitor of monoamine-oxidase-A (RIMA) and has been extensively evaluated in the treatment of a wide spectrum of depressive disorders and less extensively studied in anxiety disorders.

There is a growing evidence that moclobemide is not inferior to other antidepressants in the treatment of subtypes of depression, such as dysthymia, endogenous (unipolar and bipolar), reactive, atypical, agitated, and retarded depression as with other antidepressants limited evidence suggests that moclobemide has consistent long-term efficacy.

5.2.1.1. Pharmacodynamics

5.2.1.1.1. Action mechanism

Moclobemide is a substrate of CYP2C19. Few clinically significant drug interactions between moclobemide and teother drugs have been reported in spite of the fact that it acts as an inhibitor of CYP1A2, CYP2C19, and CYP2D6. Switch to another antidepressants could be quick as its half-life in plasma is short, 24 hours. As it is well-tolerated, therapeutic doses can be reached rapidly upon onset of treatment. After one week following dose adjustment plasma levels are reached. Patients with severe hepatic impairment require dose adjustment, not those with renal dysfunction.

5.2.1.1.2. Pharmacological profile and pharmacokinetics

A positive correlation between the plasma concentration of moclobemide and its therapeutic efficacy has been found. Due to negligible anticholinergic and antihistaminic actions, moclobemide has been better tolerated than tri or heterocyclic antidepressants.

5.2.1.1.3. Side effects and toxicology

Side effects such as dizziness, nausea, and insomnia were more frequent with moclobemide than with placebo. Sexual dysfunction and gastrointestinal side effects are much less frequent with moclobemide than with SSRIs. Gastrointestinal side effects and, especially, sexual dysfunction were much less frequent with moclobemide than with SSRIs. After multiple dosing the oral bioavailability of moclobemide reaches almost 100% [15].

5.2.1.1.4. Drug and food interactions

Moclobemide has propensity to induce hypertensive crisis after ingestion of tyramine-rich food like cheese, so dietary restrictions are mandatory.

5.2.1.1.5. Use in children and adolescents

No use in children and adolescent has been reported in clinical trials.

5.2.1.1.6. Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have had a substantial role in the pharmacotherapy of children and adolescents over the past three decades. However its efficacy has been unproven in major depression. Considering the current epidemiologic estimates of the prevalence of child

and adolescent mental disorders, as many as 10% of children in the USA, may have a potentially TCA-responsive disorder [12]

Most common tryciclic antidepressants are: Amitriptyline, clomipramine, doxepin, opipramol, trimipramine, imipramine and nortriptyline.

5.3. Amitriptyline

5.3.1. Pharmacodynamics

Amitriptyline is a tricyclic agent with sedative effects. Amitriptyline is thought to be a potent inhibitor of noradrenergic reuptake at the adrenergic nerve endings [17].

5.3.2. Pharmacokinetics

Amitriptyline is completely but slowly absorbed by the gastrointestinal tract after oral administration, and peak plasma concentration are usually reached within 4–8 hours. Amitriptyline has hepatic extensive elimination, and its systemic bioavailability ranges from 33 to 66% after oral administration [18]. In 24 hours, about one-third to one-half of the drug will be excreted. The plasma half-life ranges from 10 to 28 hours.

5.3.3. Drug and food interactions

Amitriptyline is widely distributed throughout the body and extensively bound to plasma and tissue proteins. It has got a highly lipophilic compound [17].

5.3.4. Side effects and toxicology

Amitriptyline most common side effects are blurred vision, constipation, and dry mouth which are due to anticholinergic effects. Due to the blockage of histamine receptors, it may cause sedation. In high doses, amitriptyline has cardiac effects such as dysrhythmia, prolonged conduction time, and sinus tachycardia [18].

5.3.5. Use in children and adolescents

No clinical trials on children and adolescents have been conducted with this drug.

5.4. Clomipramine

Clomipramine (Anafranil) was the first drug to obtain Food and Drug Administration (FDA) approval for treating OCD. It is a tricyclic antidepressant (TCA) with a potent ability to inhibit serotonin reuptake; it also inhibits the reuptake of norepinephrine, and has dopamine-blocking effects [19].

5.4.1. Pharmacokinetics

Clomipramine is completely but slowly absorbed by the gastrointestinal tract after oral administration, and peak plasma concentration are usually reached within 4–8 hours. It has

hepatic extensive elimination, and its systemic bioavailability ranges from 33 to 66% after oral administration [18]. In 24 hours about one-third to one-half of the drug will be excreted. The plasma half-life ranges from 10 to 28 hours.

5.4.2. Side effects and toxicology

The most common side effects of clomipramine are blurred vision, constipation, and dry mouth which are due to anticholinergic effects. It may cause sedation. In high doses, clomipramine has cardiac effects such as dysrhythmias, prolonged conduction time, and sinus tachycardia [18].

5.4.3. Use in children and adolescents

No clinical trials have been conducted in children and adolescents.

6. Other antidepressants

6.1. Vortioxetine

6.1.1. Pharmacodynamics

Vortioxetine has a dual mechanism for depression. First, it inhibits serotonin reuptake by inhibition of serotonin transporter. Second, Vortioxetine is a partial agonist of 5-HT_{1B}, 5-HT_{3}, 5-HT_{7}, 5-HT_{1D}, and HT_{1A}.

These actions modulate serotonin neurotransmitter system and, to a lesser extent, in other systems like dopamine, norepinephrine, histamine, gamma amino butiric acid (GABA) and glutamate.

6.1.2. Pharmacokinetics

Vortioxetine is well absorbed and unaffected by food. Bioavailability is about 75%. It is mainly metabolized by cytochrome P450 2D6 to two metabolites, which are not active. Renal elimination is the main route of excretion (59%) followed by fecal excretion (26%). The half-life is about 66 hours.

6.1.3. Drug and food interactions

- Tramadol increases the risk of seizures in patients taking antidepressants.
- It can cause a fatal "serotonin syndrome" when combined with MAOIs. One should not start treatment with vortioxetine at least until two weeks after stopping the MAOI.
- It can displace drugs with strong protein (e.g., warfarin) union.
- CYP450 2D6 potent inhibitors like bupropion or quinidine could increase plasma concentrations of vortioxetine.

6.1.4. Side effects and toxicology

- Gastrointestinal: nausea is the most common side effect. Other effects like decreased appetite, diarrhea, constipation, and dry mouth could also occur.
- Central nervous system: dizziness, bruxism and abnormal dreams.
- Skin: itching and, rarely, night sweats.
- Flushing (rare).
- Vortioxetine has no sexual side effects.

6.1.5. Use in children and adolescents

At this moment, some phase II clinical trials are being developed to test efficacy and tolerability of vortioxetine in pediatric patients.

6.2. Bupropion

Bupropion is a dopamine and norepinephrine reuptake inhibitor that belongs to a second-generation group of antidepressants. Bupropion has shown good results for treating major depressive disorder according to measures like the Hamilton Depression Rating Scale, and the Clinical Global Impression Severity and Impairment Scales. Its efficacy is similar to most other common antidepressants and it has an acceptable profile and good tolerability. Bupropion has shown to have a minimal effect on sexual function, and similar or even lower rates of somnolence than placebo, and it has shown lower rates of weight gain and sedation than some other commonly used antidepressants. Bupropion has indication to treat MDD in the USA, Canada, and many countries in Europe, although none of the studies has been conducted to address its safety and effectiveess in children and adolescents [11].

6.2.1. Pharmacodynamics

Chemically, bupropion is a **monocyclic phenylbutylamine** of the **aminoketone group**, which could be associated with an effect of profile different from that of other antidepressant drugs. It is also known as amfebutamone. Its primary action mechanism is neuronal reuptake inhibition of norepinephrine and dopamine without significant serotonergic effects. Bupropion lacked anticholinergic and direct sympathomimetic activity and its cardiac depressant activity is at least 10 times lower than that shown with tricyclic antidepressants.

6.2.2. Pharmacokinetics

Administration of bupropion is oral and it has been absorbed by the intestine. It has got a low molecular weight and a good liposolubility. Its half-life, in the modified release formulation, is 21 hours. The drug is metabolized in the liver and it is excreted through the kidney. The stale plasma concentration of the drug and its active metabolites are reached at 5–7 days after initiation of its administration. It is metabolized in the liver by the cytochrome P450

(CYP) 2B6, that catalyzes the hydroxylation of the side chain to form an active metabolism, the hydroxybupropion. It is excreted through the kidney.

6.2.3. Drug and food interactions

Drugs that inhibit the CYP450 2B6 such as clopidogrel and ticlopidine (antiplatelet) and valproate may have an effect of reducing the proportion between hydroxybupropion and bupropion, observing up to 68% reduction in the case of clopidogrel and up to 90% in the case of ticlopidine. Due to the important contribution of hydroxybupropion in the clinical efficacy of bupropion, it may be affected by this interaction. Concurrent use of bupropion with tobacco, alcohol, phenobarbital, and carbamazepine, furthermore, could induce the production of its active metabolite, the hydroxybupropion.

6.2.4. Use in children and adolescents

No use in children and adolescent has been reported in clinical trials.

6.3. Reboxetine

6.3.1. Pharmacodynamics

Reboxetine is a selective norepinephrine (noradrenaline) reuptake inhibitor with indication to treat depression in many European countries, but the application of approval was rejected in the USA. Reboxetine mainly acts by binding to the norepinephrine transporter and blocking reuptake of extracellular norepinephrine. The drug is indicated for the acute treatment of depressive illness or major depression and for maintaining the clinical improvement in patients initially responding to treatment [16].

6.3.2. Pharmacokinetics

Reboxetine has potent antidepressant activity, low affinity for alpha-adrenergic and muscarinic receptors, and low toxicity in animals. Humans rapidly absorb reboxetine (tmax about 2 hours) with a terminal half-life of elimination (t1/2) of 13 hours, allowing twice-daily administration. Food does not affect bioavailability. Elimination is principally renal of therapeutic actions and is usually not immediate, but often delayed 2–4 weeks. If it is not working within 6–8 weeks for depression it may require a dosage increase or it may not work at all [16].

6.3.3. Drug and food interactions

Multiple dosing, gender, or liver insufficiency had no significant effects on the pharmacokinetics. Elderly (particularly frail elderly) patients and patients with severe renal impairment may need dose reduction. Reboxetine shows no clinically relevant interaction with lorazepam and has no inhibitory effects on the major enzymes involved in drug metabolism [16].

6.3.4. Use in children and adolescents

No use in children and adolescents has been reported in clinical trials.

7. Conclusions

Fluoxetine has shown reduced depressive symptoms in young people under 18 in randomized clinical trials, although the extent up to this reduction is clinically significant and remains uncertain. In spite of this, fluoxetine is still considered the best option when a pharmacological treatment is indicated. In the therapeutic plan of young people with major depressive disorder, clinical guidelines recommend psychotherapy (especially cognitive-Behavioral therapy or interpersonal therapy) as the first-line intervention, and fluoxetine only in moderate-to-severe depressed patients who cannot access psychotherapy or have not responded to nonpharmacological approaches. Antidepressants are not well studied in this population, and further research is needed on antidepressants in young people. In all cases when a patient is started on antidepressants, he/she should be carefully monitored in prevention of risk of suicidal thoughts or attempts [10].

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