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New Antidepressant Medication: Benefits Versus Adverse Effects

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Additional information is available at the end of the chapter

Abstract

Depression [major depressive disorder (MDD)] is a mood disturbance of multifactorial origin, associated with high rates of morbidity and mortality, lack of work productivity, adverse health behaviors, and increased healthcare expenses. MDD is a leading cause of suicide, and it affects the prognosis of chronic conditions (heart diseases, diabetes, and cancer, among others). Current pharmacological treatment for MDD covers different classes of drugs, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants. The aim of this chapter is to review the literature, highlight the side effects of newer antidepressants, and especially point out the most important aspects of the latest agents approved for the treatment of MDD in adults: desvenlafaxine, levomilnacipran, vilazodone, and vortioxetine. Desvenlafaxine is a SNRI and the primary active metabolite of venlafaxine; also a SNRI, levomilnacipran is an enantiomer of the racemate milnacipran. Vilazodone and vortioxetine are multimodal antidepressants, which combine SSRI activity with additional receptor activity. Although they have proven efficacy in treating MDD and are being investigated for other possible indications, further detailed clinical trials are needed to establish their pharmaco-toxicological profile, following prolonged administration in patients who may suffer from various comorbidities.

Keywords: antidepressant, side effects, desvenlafaxine, levomilnacipran, vilazodone, vortioxetine

1. Introduction

Depression [major depressive disorder (MDD)] is a pathological affective disorder character-ized by the presence of various emotional, physical, behavioral, and cognitive symptoms, with variable duration of manifestations, with progressive evolution toward worsening, and with a high frequency of comorbidities [1, 2].

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, the clinical symptomatology includes a series of manifestations lasting more than 2 weeks: depressed mood, diminishing interest in current activities (home and work), lack of pleasure and energy, permanent fatigue, loss of confidence and self-esteem, feelings of guilt, inability to make decisions, lack of initiative, loss of attention and concentration, sleep disturbances (insomnia or hypersomnia), appetite disturbances, weight gain, modification of psychomotor activity, and recurrent thoughts of death. The symptoms are not caused by a substance or another medical condition [3–5].

To determine the severity of depressive symptoms, a number of depression rating scales are available. Montgomery-Asberg Depression Rating Scale, Hamilton Depression Scale, and Young Mania Rating Scale are clinician-administered scales. In addition, self-administered scales can be useful (Patient Health Questionnaire, Beck Depression Inventory, Zung Self-Rating Depression Scale, and Mood Disorder Questionnaire) [6, 7].

The treatment of MDD is based on pharmacotherapy, which includes numerous drugs with various structures and mechanisms of action.

The aim of this chapter is to review the literature, highlight important aspects regarding the main incriminated theories of depression and the side effects of agents used to treat MDD, and especially point out the most relevant details of the latest antidepressant drugs.

This chapter synthetizes the classic and modern features concerning the MDD pathophysiology and treatment, as well as the information about the newest antidepressants introduced in the therapy (desvenlafaxine, levomilnacipran, vilazodone, and vortioxetine), detailing the mecha-nism of action, pharmacokinetic aspects, their side effects, and benefits. The first two substances have similar mechanisms of action to existing medications, and the other two compounds are multimodal antidepressants, which combine SSRI activity with additional receptor activity.

2. Pathophysiology of depression

Literature data highlighted that the pathophysiological mechanisms involved in the manifes-tation of affective disorders are mediated by numerous neurotransmitters, such as norepineph-rine, serotonin, dopamine, acetylcholine, gamma-aminobutyric acid, and glutamate. In order to explain the phenomena that occur in the depression, several theories have been issued depending on the neuro-mediators involved in the pathogenic links, responsible for the devel-opment of the behavioral disturbances [8].

Monoaminergic theory of depression postulates that depressive manifestations are caused by the lack of one or more of the three essential neuro-mediators (serotonin, dopamine, norepinephrine) from the central nervous system synapses. These areas are situated especially in the cortex of the frontal lobe (dorsolateral, prefrontal, and orbitofrontal), the self-processing headquarters. In these areas, regional atrophy and atrophic alterations were observed, following the stress associated with the hypothalamic-pituitary-adrenal axis [8, 9].

Different types of deficits modulate the characters of depression:

- Serotonin deficiency causes in particular: sadness and thoughts with mainly negative content [8].

- Noradrenaline deficiency is associated with the diminution of voluntary and involuntary motor behaviors: the patient speaks slowly, in a monotone voice with low intensity, as if his energy is exhausted at each joint; the mimic and the gestures diminish; the posture begins to sketch the defense; the limbs are brought down (the generalized flexion tendency or even the genital posture appears); the patient's mobility decreases; in the beginning, the gestures of social and family significance are not performed; and the patient lacks personal hygiene behavior [10, 11].

- Dopamine deficiency is manifested by anhedonia; the patient can no longer enjoy any of the things that previously used to cause pleasure. From the outset, it should be noted that the therapeutic response appears differently for the three components. Often, the first neuro-mediator involved in the response is norepinephrine. Serotonin responds a little bit later. The patient regains his motor skills, before the ideation has normalized. This situation, in which the patient has the power to practice negative thoughts, appears in the early weeks of antidepressant therapy onset and is responsible for the suicidal accidents that may occur [9]. In conclusion, people with inhibited depression should be closely monitored during the first 3 weeks after the therapy is established.

A therapeutic response consists of 50% alleviation of the symptoms following administration of the antidepressant medication. A small percentage of people may develop resistance to antidepressants (through lack of synthesis or transport or excess metabolism of one or more monoamines). These patients are recommended to either potentiation of the treatment or electroconvulsive therapy, as a solution for achieving remission of the depression.

In these conditions, the therapeutic targets of currently used antidepressant drugs are aimed at augmenting the monoaminergic deficiency at the synaptic level.

This response can be achieved by:

- The action on the receptor level

- The receptor stimulation through neuro-mediator release

- Inhibition of the reuptake pump or inhibition of the metabolism enzyme

There is also evidence for the involvement of other (secondary) systems in the pathogenesis of depression, with the participation of acetylcholine, somatostatin, leptin, substance P, thyrotropin-releasing hormone (TRH), **brain-derived neurotrophic factor** (BRNF), gamma-aminobutyric acid (GABA), and glutamate [12].

It should be underlined that the reduction of any monoaminergic neuro-mediator is accompanied by upregulation events that increase the reactivity to small amounts of monoamine: this could be the mechanism responsible for hyper-serotoninergic reactions (serotoninergic pseudo-syndrome) manifested at the beginning of the treatment, with monoaminergic augmentation in persons with serotonin deficiency.

3. Treatment of depression

This affective disorder, which has a very long evolution, is generally underdiagnosed and insufficiently treated, statistical data showing that currently only half of the persons affected by depression have undergone pharmacological or non-pharmacological treatment. Despite the fact that 80–90% of cases of depression can be successfully treated, this disease considerably affects the quality of life of both patient and his family.

It is particularly important to early diagnose depression and rapidly establish the appropriate therapy to reduce the consequences of this pathological condition on the general (physical and mental) status of the patient.

Management of depression is complex, including therapeutic lines with targeted action on associated organic pathology, psychotherapy with the final goal of rebalancing the patient [13]. The treatment of affective disorders is of long duration and individualized, involving an adequate cooperation between doctor, patient, and his family for the choice of the appropriate antidepressant drug from a pharmacological and economical point of view.

Modern treatment of depression combines pharmacotherapy with alternative methods (represented by psychotherapy, hypnosis, cognitive behavioral treatment, interpersonal therapies). Short-term psychotherapeutic approaches, especially cognitive behavioral methods and interpersonal therapies, have been shown to be highly effective in relieving symptoms and diminishing the number of depressive episodes [14, 15]. More obvious results are obtained by combining psychotherapy with pharmacotherapy, which consists of the administration of antidepressants, their efficiency being demonstrated in 80% of depression cases. The pharmacodynamic effects of antidepressants occur after a period of time ranging from 2 to 4 weeks, during which psychotherapy has beneficial effects [16, 17].

It is known that in many cases the patients are rapidly discontinuing medication, conditions in which psychotherapy exhibits beneficial effects by increasing the patient's compliance/adherence, resulting in diminution or even elimination of the sense of isolation, as well as the powerless and hopeless feelings. These results improve communication with the patient, who becomes more conscious that stopping the administration of recommended drugs can lead to a recurrence of the disease. There are a lot of tools like questionnaires or patient-reported outcomes (PROs) that identify some different patterns of behavior of patients with depression with the aim of improving patients' adherence [18].

Depending on the clinical manifestations experienced by the patient (anxiety, insomnia, psychotic symptoms), antidepressant medication may be combined for limited periods of time with anxiolytic, sedative, or antipsychotic drugs. If affective disorders heavily respond to classical antidepressants, mood-stabilizing agents, electroconvulsive therapy, or bright light therapy may be associated.

3.1. Pharmacotherapy

A wide range of antidepressants are available nowadays, belonging to various therapeutic classes, with various mechanisms of action, effective in some affective disorders, but also a host of adverse effects as well as the possibility of interacting with other prescribed medications. In selecting the antidepressant, it is necessary to balance, on the one hand, its effectiveness in the affective disorder, and on the other hand, the adverse effects may occur (mild, moderate, severe, temporary, or lasting).

Table 1 summarizes the adult doses and some side effects of selected antidepressants (seizures and conduction abnormalities are dose-dependent side effects) [19].

Some of the antidepressant medication side effects may be unpleasant, others are dangerous to the patient, and they should be reported to the physician, who will decide to replace the drug or to adjust the dose. It is necessary to mention that, apart from specific adverse reactions, all antidepressants present a risk of suicide, especially at the beginning of treatment; therefore, the patient should be supervised and supported by family and entourage.

3.1.1. Classical antidepressants (first generation)

- Monoamine oxidase (MAO) inhibitors (MAOIs)

These agents inhibit the metabolism of monoamines (but not their synthesis) and release norepinephrine from postganglionic deposits (mebanazine, tranylcypromine, phenelzine) [20].

They have low selectivity, inhibiting other enzymes including dopamine-B-oxidase, diamine oxidase, amino acid decarboxylase, and choline dehydrogenase, which are responsible for some of the side effects of the group. Some of them act selectively for only one of the two MAO forms, the MAO-A: moclobemide, miaprine, pirlindole, and toloxatone [21]. The MAO-B inhibitors, such as selegiline and rasagiline, are reserved for Parkinson's disease therapy [22]:

- Irreversible, long-acting, noncompetitive inhibitors (phenelzine, tranylcypromine), of both MAO-A and MOA-B subtypes

- Reversible, short-acting, MAO-A selective inhibitors (moclobemide, brofaromine) that are experienced in Canada

MAOIs were among the first antidepressant drugs to be clinically introduced, which are used nowadays much less than other antidepressants because of their toxicity and serious drug and food interactions [23, 24].

For most of MAOIs, the enzyme blocking takes 2–6 weeks (new enzyme synthesis occurring only after 2 weeks) [25]. During this time, the administration of drugs that augment the monoamines' level (such as tricyclic antidepressants, fluoxetine, naphazoline, xylometazoline,

Drug	Initial dose (mg/day)	Usual dosage range (mg/day)	Side effects				
			Anticholinergic effects	Sedation	Orthostatic hypotension	Seizures	Conduction abnormalities
Amitriptyline	25	100–300	4+	4+	3+	3+	3+
Bupropion	150	150–300	+	0	0	4+	+
Citalopram	20	20–40	0	+	0	2+	2+
Desipramine	25	100–300	2+	2+	2+	2+	2+
Desvenlafaxine	50	50	+	+	0	2+	+
Doxepin	25	100–300	3+	4+	2+	3+	2+
Duloxetine	30	30-90	+	0	+	0	0
Escitalopram	10	10–20	0	0	0	0	0
Fluoxetine	20	20–60	0	0	0	2+	0
Fluvoxamine	50	50–300	0	+	0	2+	0
Imipramine	25	100–300	3+	3+	4+	3+	3+
Mirtazapine	15	15–45	+	2+	2+	0	+
Nefazodone	100	300–600	0	3+	3+	2+	+
Nortriptyline	25	50–150	2+	2+	+	2+	2+
Paroxetine	20	20–60	+	+	0	2+	0
Sertraline	50	50–200	0	0	0	2+	0
Trazodone	50	150–300	0	4+	3+	2+	+
Venlafaxine	37.5–75	75–225	+	+	0	2+	+

0, absent; +, very low; 2+, low; 3+, moderate; 4+, severe.

Table 1. Antidepressant drugs: adult doses and selected side effects [19].

or other drugs) or ingestion of food containing tyramine, the catecholamine precursor, can generate severe increase in blood pressure and death. In this situation, the intestinal fermented tyramine can be transported in blood and replaces norepinephrine in the vesicles, resulting in amplification the effects of the normal norepinephrine stimulation [26].

The main side effects of nonselective MAOIs are "cheese reaction" (severe hypertensive response to tyramine-containing foods, such as cheese, beer, wine, liver, sardines, well-hung meat, yeast, or soybean derivatives), anticholinergic side effects (dry mouth, blurred vision, urinary retention, etc.), postural hypotension, insomnia, weight gain, sexual side effects, convulsions (in overdose), and hepatotoxicity (rare). Nausea, insomnia, and agitation, but no "cheese reactions," were reported for moclobemide [19, 23].

- Tricyclic antidepressants are divided into subgroups with similar general structures:

  - Imipramine, desipramine, clomipramine, trimipramine, amitriptyline

  - Nortriptyline, butriptyline, doxepin, protriptyline [16]

- Tricyclic antidepressants have the following mechanisms of action:
  - Inhibition of serotonin transporter
  - Inhibition of norepinephrine transporter
  - Slight inhibition of dopamine reuptake
  - Stimulation 5-HT1A receptors
  - Inhibition of 5-HT2A receptors (but also affinity for 5-HT6 and 5-HT7 receptors)
  - Inhibition of alpha-1 receptors [27]

3.1.2. Heterocyclic antidepressants (second or third generation)

- With nonselective action on the amine neurotransmitters
- With anticholinergic effects (maprotilin, nomifensine, amoxapine)
- Without anticholinergic effects (venlafaxine, bupropion)
  - Heterocyclic antidepressants have the following mechanisms of action:
- Inhibition of alpha-2 receptors
- D2 receptor stimulation
- Inhibition of H1 receptors (for some compounds even H2 receptors)
- Inhibition of muscarine receptors
- Blockade of sodium and calcium channels (being responsible for cardiotoxicity) [16]

Various mechanisms of actions are responsible for the pharmacodynamic effects as well as for a lot of adverse effects, thus limiting their indications.

Adverse reactions are particularly due to the muscarine receptor blockade and consist of mucosal dryness, blurred vision, diminution of digestive tract motility, constipation, urinary retention, cognitive impairment and memory disturbances, increased body temperature, akathisia (psychological restlessness without physical agitation), tachycardia, hypotension, arrhythmias, and, in case of overdose, cardiotoxicity. Other side effects of tricyclic antidepressants include excessive sweating, paradoxical emotional changes (anxiety or the lack of emotional reactivity), modification in appetite and body weight, sexual dysfunction, muscle contraction, nausea and vomiting, and rarely rhabdomyolysis [16]:

- 5-HT2A/5-HT2C receptor antagonists (trazodone, nefazodone, mirtazapine)
- Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram)

The onset of the therapeutic effect varies from a few hours to 2–3 days after SSRI administration. The peak blood concentration is reached in 10–21 days. Some of SSRIs persist for a long time in the body, for example, fluoxetine, which is completely eliminated only after 5 weeks [17, 28, 29].

During the treatment, the upregulation of the synapses can initially trigger a pseudo-serotoninergic syndrome, with psychomotor agitation, akathisia, insomnia, tremor, muscle fasciculation, fever, and vomiting. This syndrome is sensitive to benzodiazepine therapy, and usually the spontaneous resolution appears within a few days [16, 23].

Pure serotonin syndrome is particularly common for tricyclic antidepressants, more rarely for SSRIs, and most commonly occurs in drug combinations with metabolic inhibitors or with agents that may increase the serotonin level. Serotonin syndrome is manifested by agitation, confusion, excessive sweating, mydriasis, muscle spasms or muscle incoordination, fever, seizures, and coma.

The therapy with SSRIs is long-lasting, with the shortest treatment indicated being 3–6 months. As expected, a degree of dependence occurs; therefore, avoiding sudden discontinuation of treatment with SSRIs is essential. Otherwise insomnia, agitation, confusion, trembling, anxiety, and even hallucinatory phenomena may occur during treatment [30]:

- Mixed serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran)

- Dopamine and norepinephrine reuptake inhibitors (bupropion—reserved especially for asthenic and dopamine deficiency cases)

- Norepinephrine reuptake inhibitor (reboxetine)

- Serotonin disinhibitor and alpha-2 antagonists (mirtazapine)

- Serotonin antagonist and reuptake inhibitors (nefazodone, trazodone) [16, 23]

Among the antidepressant groups, SSRIs and SNRIs are preferred because not only of their therapeutic efficacy but also of the relatively small number and decreased severity of adverse effects [28, 30, 31].

4. Desvenlafaxine

The *O*-desmethylvenlafaxine or desvenlafaxine, a RS-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol derivative, is the synthetic agent of the main active metabolite of venlafaxine. First of all, it was obtained as desvenlafaxine succinate (Pristiq®) and marketed by the company Wyeth Pharmaceuticals, which was subsequently acquired from the American corporation Pfizer [32]. This principal metabolite is 70% produced following the biodegradation of venlafaxine, the two drugs having similar demonstrated pharmacodynamic effects [33].

The development of desvenlafaxine was performed in hoping to improve the pharmacokinetic and clinical profile of the parent substance. It was approved as antidepressant drug by the FDA in February 2008, being available for medical use, in the treatment of MDD in adult patients, in May 2008 [34].

This agent was also experienced for the nonhormonal therapy of menopausal disorders associated by mild-to-serious vasomotor symptoms and in some types of anxiety [35, 36]. At the

beginning of 2008, a product containing desvenlafaxine (Ellefore) was withdrawn from the market in the European Union, due to its insufficient documentation and clinical experience; but later in 2012, Pfizer corporation obtained the authorization for the use of Pristiq® in Spain. It also received the market authorization in Canada for the pharmacotherapy of depression in February 2009. A few years later, FDA approved the use of both brand and generic products containing desvenlafaxine fumarate (Desvenlafaxine fumarate, 2013) [37].

4.1. Pharmacological properties

In vitro studies revealed that desvenlafaxine determines the inhibition of serotonin and norepinephrine reuptake (10 times more potent for serotonin than for norepinephrine), thus blocking the removal of the main mediators (serotonin, norepinephrine) that affect mood, increasing their concentration at the synaptic level [32, 38]. No notable influence on muscarine, histamine, or alpha-1 adrenergic receptors and on the activity of monoamino oxidase was proven. Moreover, the lack of the influence on the functionality on sodium, potassium, chloride, or calcium ion channels was also evidenced [34, 39].

Dosage forms		50 mg, light-pink square pyramid extended-release tablet (containing 76 mg of desvenlafaxine succinate) 100 mg, reddish-orange square pyramid extended-release tablet (containing 152 mg of desvenlafaxine succinate)
Administration		Orally, once daily, with or without food
Dosage		Initial dosage of 50 mg, approximately at the same moment of time, each day, maintenance dose of 50 mg; the maximum accepted daily dose is 400 mg
Absorption		Not influenced by food intake
Time to maximum concentration		7.5 hours
Bioavailability		80% (being not influenced by the meals)
Protein-binding percentage		30%
T1/T2		Approximately 11 hours
Steady-state plasma concentrations		Achieved within 4–5 days after oral administration of a unique dose
Volume of distribution		3.4 L
Metabolism	Is mainly conjugated (via uridine 5′-diphospho-glucuronosyltransferase participation) and secondarily is metabolized by oxidation (through N-demethylation)	CYP3A4 CYP2D6 is not involved
Elimination		45% is eliminated and unchanged in urine, 72 hours after oral administration

Table 2. Pharmacological aspects of desvenlafaxine [32, 34, 38–41].

The drug is available as extended-release tablets for oral administration, which contain desvenlafaxine succinate (**Table 2**).

4.2. Side effects of desvenlafaxine

Current safety and efficacy information for the treatment of MDD highlights that most patients have well responded and tolerated and did not experience severe side effects to desvenlafaxine [42].

The most often described side effects of desvenlafaxine were nausea, vomiting, dry mouth, constipation, fatigue, headache, dizziness, insomnia, decreased appetite, hyperhidrosis, erectile dysfunction, and delayed ejaculation in men (**Table 3**) [34, 42].

Of these, the frequent adverse reactions, such as nausea, vomiting, dizziness, and headache, observed in short-term trials of up to 8 weeks in patients treated with desvenlafaxine (Pristiq®, Wyeth), usually lead to discontinuation of the treatment. The other side effects of the desvenlafaxine were related to the drug-drug interactions or to the presence of liver or kidney dysfunctions [38, 43].

4.3. Differences between desvenlafaxine and venlafaxine

Literature data highlighted some pharmacological differences between these two antidepressant drugs, but the therapeutic experience did not reveal substantial advantages of desvenlafaxine over venlafaxine use in the treatment of MDD.

System and organ	Manifestations
Cardiovascular	Palpitations, hypertension, tachycardia, hot flushes, orthostatic hypotension, peripheral coldness
Hematologic	Abnormal bleeding
Gastrointestinal	Nausea, vomiting, dry mouth, constipation, diarrhea, increase in transaminase levels
Nervous system	Dizziness, headache, insomnia, somnolence, tremor, paresthesia, dysgeusia, disturbance in attention, tinnitus, vertigo, depersonalization, hypomania, syncope, withdrawal syndrome, anxiety, abnormal dreams, nervousness, seizures, convulsions, extrapyramidal symptoms, serotonin syndrome
Genitourinary	Urinary hesitation, proteinuria, decreased libido, anorgasmia, anorgasmia, abnormal orgasm, erectile dysfunction, delayed ejaculation, ejaculation disorders in men, ejaculation failure
Respiratory	Yawning, epistaxis, interstitial lung disease, eosinophilic pneumonia
Skin	Hyperhidrosis, rash
Musculoskeletal	Musculoskeletal stiffness
Metabolic and endocrine	Decreased weight, increased blood cholesterol, decreased appetite, increased blood triglycerides, increased blood prolactin, hyponatremia
Others	Hypersensitivity reactions, fatigue, feeling jittery, blurred visions, mydriasis

Table 3. The most frequent adverse effects of desvenlafaxine [34, 38, 42, 44–46].

Preclinical and clinical investigations argue that venlafaxine and desvenlafaxine are basically equivalent, from the pharmacological point of view, even if there were observed dissimilarities, regarding especially the pharmacokinetic profile, dose regimen, and the drug interactions.

The most important differences between venlafaxine and desvenlafaxine are the following:

- Both antidepressant drugs present the similar mechanism of action, consisting of inhibition of serotonin and norepinephrine reuptake, but the desvenlafaxine's binding affinity at norepinephrine reuptake pumps is higher than venlafaxine's; yet this effect did not prove a therapeutic relevance [47].

- The clinical trials communicated similar tolerability and comparable incidence of adverse effects in patients treated for depression [48, 49]. Different clinical trials, performed during 8 weeks, revealed the superior efficacy of 100 and 400 mg, but not of 200 mg of desvenlafaxine (Pristiq®, Wyeth), on the improvement of depression symptomatology, clinically evidenced and assessed using Hamilton Depression Scale, and also the effectiveness of 400 mg on the remission rates, compared to placebo [36, 45, 50–52].

- The parent substance, venlafaxine, undergoes primarily biodegradation by the CYP 2D6-mediated oxidative reactions, to be converted into O-desmethylvenlafaxine, while desvenlafaxine is mainly inactivated by glucuronidation and secondarily metabolized by oxidation (through N-demethylation) to N,O-didesmethylvenlafaxine, its biodegradation being not influenced by the enzymatic system of cytochromes P450 (CYP 2D6) [40, 41]. Taking into account these issues, it was suggested that desvenlafaxine may be an advantageous option in patients with genetic polymorphisms of CYP2D6 (such as poor metabolizers) [34].

- As a result of the fact that desvenlafaxine has no markedly effect on CYP2D6, at therapeutic doses, it has lower risk of drug interactions, compared to venlafaxine, being preferred to prevent possible drug-drug interactions with CYP2D6 substrates (e.g., SSRIs, tricyclic antidepressants, several beta-blockers, quinidine, opioids). However, there are inconsistent evidences that desvenlafaxine would be more effective, better tolerated, or safer than venlafaxine in clinical use [40, 41, 44, 50].

- On the other hand, the treatment with desvenlafaxine may have a benefit, in terms of simpler dosage regimen compared with venlafaxine (small initial dose and lower minimum therapeutic dose), with more anticipated drug levels [45]. The FDA recommendations mention the indication of using the same 50 mg starting, and maintenance doses, for the treatment with desvenlafaxine, while the administration of extended-release form of venlafaxine needs titration from the starting dose of 37.5 mg per day to the maintenance dose of 150–225 mg per day [51]. The practical aspect is related to the fact that desvenlafaxine dosage choosing is based on the experience gained from several 8-week acute-phase clinical studies, but the real therapeutic response is not generally obtained in this short interval of time [34].

5. Levomilnacipran

Levomilnacipran, a (1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropane-1-carboxamide derivative, is the levo-enantiomer (1S, 2R-milnacipran) of racemate milnacipran, approved in 2009 for the treatment of fibromyalgia [53, 54]. It was discovered by Pierre Fabre Laboratories, France, and coproduced by Forest Laboratories, Inc. (Fetzima™), being approved by the FDA to be used for the treatment of MDD in adult patients in the United States and Japan in July 2013 and in Canada in May 2015 [55, 56]. It is not available on the market in the European Union and Australia.

The researches performed in laboratory animals showed that levomilnacipran is the pharmacologically more active enantiomer of the racemic mixture milnacipran, having 50, respectively, and 13 times more intense inhibitory activity on the norepinephrine and serotonin reuptake pumps, a higher peak blood concentration and a prolonged elimination half-life compared with the other enantiomer 1S,2R-milnacipran (coded F2696) [56–59].

Currently, it is under clinical research as a therapy of anxiety, bipolar disorders, post-traumatic stress diseases, vasomotor symptoms associated with menopause, peripheral neuropathy (especially associated with diabetes mellitus), and chronic musculoskeletal pain. Levomilnacipran has also been investigated for the treatment of fibromyalgia and phantom limb syndrome but was not approved to be used for these purposes [56].

5.1. Pharmacological properties

In vitro studies revealed that levomilnacipran determines the strong and selective inhibition of serotonin and norepinephrine reuptake transporters (two times more potent and selective for norepinephrine than for serotonin), with a consequent increasing of these mediator concentration in the central nervous system [60]. It proved to have a more balanced reuptake of both serotonin and norepinephrine compared to other known SNRIs [56, 61]. Due to this difference in the selectivity action on these neurotransmitters, it was postulated that levomilnacipran may be beneficial in MDD related to the norepinephrine deficiency, with the demonstrated improvement of core symptoms and, consequently, the patient social and occupational activities [62–64]. It may also be useful in refractory depression or in the cases susceptible to potential increase of weight gain during chronic therapy with other antidepressant drugs [61].

Levomilnacipran provides a "two and a half" action, the inhibition of the norepinephrine transporter facilitating the action of dopamine, as long as this mediator diffuses through the synapses, without requiring the presence of a transporter. No important activity on dopamine, serotonin (5-HT1–5-HT7), muscarine, histamine, and alpha- or beta-adrenergic and opioid receptors and no inhibitory effects on the monoamino oxidase were evidenced. The lack of affinity on the sodium, potassium, chloride, or calcium ion channels was also observed [56].

Recent researches highlighted the inhibitory action of levomilnacipran on the `beta-site amyloid precursor protein cleaving enzyme-1`, known to be responsible for the formation of β-amyloid plaque, thus arguing its possible use in the treatment of `Alzheimer's disease` [64].

The drug is available as extended-release capsules for oral administration, which contain levomilnacipran hydrochloride (**Table 4**).

5.2. Side effects of levomilnacipran

Short-term safety clinical trials revealed that most patients with MDD have well responded and tolerated and did not experience important side effects to levomilnacipran [62, 65]. The most common side effects of levomilnacipran were nausea, vomiting, hyperhidrosis, heart rate increase, tachycardia, palpitations, urinary hesitation, erectile dysfunction, and ejaculate disorders in men (**Table 5**) [56].

Long-term clinical studies documented that levomilnacipran manifested acceptable tolerability compared to placebo. Severe adverse reactions, such as nausea, vomiting, headache, tachycardia, hypertension, extrasystoles, and convulsion, observed in long-term trials of 48 weeks in patients treated with levomilnacipran, generally lead to discontinuation of the treatment. The other side effects of the levomilnacipran were related to the drug-drug interactions (inhibitors of CYP3A4 such as clarithromycin, ketoconazole, or itraconazole will increase its blood level) or to a concomitant hepatic, renal, and cardiac pathology. On the contrary, the association of levomilnacipran with the inducers of CYP3A4, such as rifampicin or carbamazepine, may determine a diminution of its plasma concentration [66, 67].

Dosage forms	20 mg, extended-release capsule with yellow cap and white body 40 mg, extended-release yellow-opaque capsule 80 mg extended-release capsule with pink cap and white body 120 mg, pink-opaque extended-release capsule
Administration	Orally, once daily, with or without food
Dosage	Initial dosage of 20 mg in a unique daily administration for 2 days, then increasing the dose to 40 mg per day; the maximum accepted daily dose is 120 mg
Absorption	Not influenced by food intake
Time to maximum concentration	6–8 hours
Bioavailability	92%
Protein-binding percentage	22%
T1/T2	Approximately 12 hours
Mean apparent total clearance	21–29 L/hour
Volume of distribution	387–473 L
Metabolism	Hepatic (primarily by CYP3A4); is converted primarily to two inactive metabolites: desethyl levomilnacipran and p-hydroxy-levomilnacipran with a minor involvement of CYP2C8, CYP2C19, CYP2D6, and CYP2J2
Elimination	58% of uncharged drug is excreted in the urine

Table 4. Pharmacological aspects of levomilnacipran [55, 56].

System and organ	Manifestations
Cardiovascular	Palpitations, tachycardia, hypertension, hot flushes, orthostatic hypotension, angina pectoris, supraventricular/ventricular extrasystoles
Hematologic	Abnormal bleeding
Gastrointestinal	Nausea, vomiting, constipation, sweeting, elevations in serum aminotransferase levels
Nervous system	Dizziness, headache, sleep troubles, excessive happiness or irritability, reckless behavior, nervousness, anxiety, difficulty concentrating, memory changes, confusion, weakness tremor, paresthesia disturbance in attention, drowsiness, dizziness, suicidal ideation, withdrawal syndrome, hallucinations, serotonin syndrome, seizures, convulsions, extrapyramidal symptoms, encephalopathy
Genitourinary	Urinary hesitation, decreased libido, erectile dysfunction, ejaculation disorders in men, ejaculation failure, delayed ejaculation, testicular pain
Respiratory	Upper respiratory tract infection
Skin	Hyperhidrosis, rash
Musculoskeletal	Musculoskeletal stiffness
Metabolic and endocrine	Decreased appetite, hyponatremia
Others	Hypersensitivity reactions, fatigue, blurred visions, visual disturbances, mydriasis, eye pain, swelling or redness in or around the eye

Table 5. The most frequent adverse effects of levomilnacipran [68–71].

Various preclinical researches showed the most intense antidepressant effect of levomilnacipran without substantially influencing the animal spontaneous locomotor activity, compared to other antidepressant drugs (venlafaxine, duloxetine) in different experimental animal models of depression, anxiety, and stress (such as forced swim test, tail suspension test, shock-induced ultrasonic vocalization) [70].

Short-term clinical trials highlighted the superior efficacy of levomilnacipran on depressive and disability symptoms (especially motivation and energy), and functional improvement of the patient status, compared to placebo, was quantified using the Montgomery-Asberg Depression Rating Scale, respectively, and the Sheehan Disability Scale. Significant superiority to placebo was also demonstrated by improvement of the patient's social activity, work, and family life [71–74]. On the other hand, there were insufficient and irrelevant data, regarding the efficacy for the relapse prevention in the long-term use of levomilnacipran [75].

5.3. Differences between levomilnacipran and milnacipran

Literature data indicated some pharmacological differences between these two antidepressant drugs, but the performed clinical studies did not prove considerable advantages of levomilnacipran over milnacipran use in the treatment of MDD.

There are few clinically relevant differences between levomilnacipran and milnacipran consisting of the simplicity of dose regimen, a more selective pharmacodynamic activity, an improved

pharmacokinetic profile (with less complex correlation between blood concentration and the pharmacodynamic effect), and a reduced potential for drug interactions [76, 77].

The most important levomilnacipran's advantage is its once-daily administration of a sustained-release capsule compared with the twice-daily administration tablets of milnacipran, thus improving the patient's compliance especially to chronic therapy.

6. Vilazodone

Vilazodone, 2-benzofurancarboxamide, 5-[4-[4-(5-cyano-1H-indol-3-yl)butyl]-1-piperazinyl]-, hydrochloride (1:1) [78], is a new multimodal antidepressant drug indicated in the United States for the treatment of MDD in adult patients [79]. Its discovery program began in the mid-1990s, and FDA approved it in January 2011. It also received market authorization in Mexico and Canada for MDD pharmacotherapy. Moreover, it was found that vilazodone improves psychic and somatic symptoms in generalized anxiety disorder [80–82].

6.1. Pharmacological properties

Vilazodone is an indolalkylamine with a dual mechanism of action which consists of 5-HT1A receptor partial agonist and SSRI activity. It does not bind to the norepinephrine or dopamine reuptake sites with the same high affinity [81, 83].

The most prevalent out of the 14 different structurally distinct types of 5-HT receptors in the brain is 5-HT1A, which is localized especially in the raphe nuclei (presynaptic), the hippocampus, the frontal cortex, the dorsal horn of the spinal cord, the lateral septum, and the amygdala (postsynaptic). Presynaptic 5-HT1A receptors exhibit a key role in the pathophysiology and treatment of depression and anxiety disorders. According to Sahli et al., vilazodone is 60 times more selective for the 5-HT1A receptor than buspirone (the only 5-HT1A receptor partial agonist approved as an antidepressant) and has a SSRI activity 30 times more potent than fluoxetine (the first SSRI approved by FDA for MDD therapy) [83].

The drug is available as tablets for oral administration which contain vilazodone hydrochloride (**Table 6**).

6.2. Benefits versus adverse effects

Due to its unique mechanism of action, vilazodone has the potential benefits of faster onset of action, greater efficacy, and lower adverse event risks compared with currently used antidepressants, especially lower sexual side effects [84, 85]. Preclinical studies and clinical trials showed that vilazodone exhibits a diminished incidence of sexual adverse effects and minimal weight gain, similar for vilazodone and placebo, important aspects given that patients find sexual dysfunction, weight gain, and drowsiness to be the most frequently unpleasant adverse effects induced by antidepressants [86].

Sexual dysfunction was reported in 40–70% of SSRI-treated patients [87], and SSRIs therapy can determine sexual dysfunction in all three phases of the human sexual response cycle

Dosage forms		10 mg pink, film-coated, oval tablet 20 mg orange, film-coated, oval tablet 40 mg blue, film-coated, oval tablet
Administration		Orally, once daily, with food
Dosage		Initial dosage of 10 mg for 7 days, augment to 20 mg, the dose may be raised up to 40 mg after at least 7 days between dosage increases
Absorption Tmax		4–5 hours
Peak plasma concentration		156 ng/ml
Half-life		Approximately 25 hours
Absolute bioavailability		72% (with food)
Percentage of protein binding		96–99%
Metabolism	CYP pathways	CYP3A4 (primarily), CYP2C19, CYP2D6
	Non-CYP pathways	Carboxylesterase
Elimination		Unchanged drug (1% in the urine and 2% in the feces)
Common adverse reactions (>5%)		Diarrhea, nausea, vomiting, and insomnia
Drug interactions	CYP3A4 inhibitors	Vilazodone dose should be ≤ 20 mg once daily
	CYP3A4 inducers	Augment vilazodone dosage by twofold, over 1 to 2 weeks (up to 80 mg once daily) when coadministered with strong CYP3A4 inducers for more than 14 days

Table 6. Pharmacological aspects of vilazodone [19, 78, 83].

(desire, arousal, and orgasm). SSRI-induced sexual side effects cannot only reduce patients' quality of life but also cause treatment noncompliance and discontinuation, therefore augmenting the risk of MDD relapse and recurrence [88].

The effects of vilazodone (20 or 40 mg/day) on sexual functioning were also evaluated in healthy, sexually active adults assessed using the Changes in Sexual Functioning Questionnaire (CSFQ—a self-report questionnaire with 14 items used in antidepressant trials); vilazodone proved no significant effect on sexual functioning in healthy adults [87].

In a rat sexual behavior model, acute, sub-chronic, and chronic vilazodone treatment did not cause sexual dysfunction; moreover, 1 week vilazodone administration normalized sexual function in animals which registered paroxetine-induced sexual dysfunction [88].

Another benefit of this drug is related to its effect on anxiety disorder, and studies are being conducted to assess its efficacy in generalized anxiety disorder, post-traumatic stress syndrome, and social anxiety illness [80]. As Khan et al. reported, 8-week vilazodone therapy has led to improvements in four psychic anxiety items (anxious mood, depressed mood, tension, intellectual) and five somatic anxiety items (somatic muscular, somatic sensory, respiratory, cardiovascular, and autonomic symptoms) [82].

System and organ	Manifestations
Gastrointestinal	Nausea, vomiting, diarrhea, dry mouth
Nervous system	Dizziness, headache, insomnia
Cardiovascular	Chest pain, hypertension, tachycardia, palpitations, orthostatic hypotension
Others	Fatigue

Table 7. The most frequent adverse effects of vilazodone [81, 89].

Thus, vilazodone could be beneficial for some subgroups of patients, like ones with depression and comorbid anxiety, and patients with sexual side effects on SSRIs or other antidepressant drugs [85].

The results of the research published so far have shown that vilazodone has a relatively high level of safety and tolerability in adults. The most frequent adverse effects, which were related to the sleep quality and gastrointestinal tract, were transient in nature and mild to moderate in severity (**Table 7**) [80, 81, 85].

The adverse events occurred within the first few weeks of the therapy and led to few premature discontinuations [84, 89]. Further studies are needed not only to evaluate the efficacy and tolerability profile of vilazodone in the elderly and in adolescents with MDD but also to estimate its long-term safety. Due to the lack of information in human trials, it may be administered in pregnant women and lactation only if the benefits outweigh the potential risks [83–85].

Yet some results require further research on larger groups of subjects, with different characteristics, and for longer periods of time. Yan Li et al. developed a preclinical study and registered that vilazodone diminished depression-like behavior without altering visuospatial memory after 1 month of therapy. But after 3 months of treatment, vilazodone did not alter depression-like behavior or cognition. The drug was administered in therapeutic doses in healthy middle-aged female mice, which were assessed in the forced swim test (for depression-like behavior), in novel object recognition test (for recognition memory), or in novel object placement test (for visuospatial memory). The findings support the age difference in drug response for some antidepressant drugs [90].

7. Vortioxetine

Vortioxetine, 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide [91], is another new multimodal antidepressant drug that has been approved for MDD therapy in adult patients, in September 2013 in the United States, in December 2013 in European Union, and later in Canada, South Africa, Australia, Mexico, and South Korea [80].

Besides its antidepressant properties proven in several short-and long-term studies [93], vortioxetine demonstrated pro-cognitive effects in preclinical studies, affecting learning and memory processes (enhancing hippocampal synaptic plasticity and augmenting the output of

pyramidal cells) [80, 94]. Positive results on cognitive function (memory and executive functioning) were also highlighted in clinical trials [92].

7.1. Pharmacological properties

Vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the serotonin transporter. It enhances 5-HT (more than a SSRI), NE, DA, acetylcholine, and HA levels in rat brain regions associated with MDD (like the PFC and the ventral hippocampus). Furthermore, it increases glutamatergic neurotransmission, probably through inhibiting GABA interneurons [80, 92, 94].

Its discovery program origins in the hypothesis were derived from researches of combined serotonin transporter inhibition and 5-HT1A receptor modulation; subsequently, the profile was modified toward a combination of serotonin transporter inhibition, 5-HT1A receptor agonistic activity, and 5-HT3 receptor antagonism [95].

The drug is available as immediate-release tablets for oral administration which contain the beta-polymorph of vortioxetine hydrobromide (**Table 8**).

Dosage forms		5 mg pink, almond-shaped biconvex film-coated tablet 10 mg yellow, almond-shaped biconvex film-coated tablet 15 mg orange, almond-shaped biconvex film-coated tablet 20 mg red, almond-shaped biconvex film-coated tablet
Administration		Orally, once daily, without regard to meals
Dosage		Initial dosage is 10 mg, augment to 20 mg/day, as tolerated consider 5 mg/day for patients who do not tolerate higher doses 5–10 mg/day therapy can be discontinued abruptly
Absorption Tmax		7–11 hours
Volume of distribution		Approximately 2600 L
Half-life		Approximately 66 hours
Absolute bioavailability		75% (unaffected by food)
Percentage of protein binding		98%
Metabolism	CYP pathways	CYP2D6 (primarily), CYP3A4/CYP3A5, CYP2C9, CYP2C19, CYP2C8, CYP2A6, CYP2B6
Elimination		59% in the urine and 26% in the feces, as metabolites
Common adverse reactions (>5%)		Nausea, constipation, and vomiting
Drug interactions	CYP2D6 inhibitors	Diminish vortioxetine dose by half when a strong CYP2D6 inhibitor is associated
	CYP inducers	Augment vortioxetine dose when a strong CYP inducer is coadministered for more than 14 days (up to no more than three times the original dose)

Table 8. Pharmacological aspects of vortioxetine [91, 96, 97].

7.2. Benefits versus adverse effects

Sanchez et al. reviewed preclinical studies and clinical trials and concluded that vortioxetine is different from SSRI and SNRI antidepressants on the strength of its multimodal mechanism of action, both inhibition of the potent serotonin transporter and direct modulation of 5-HT receptors [95].

Studies evaluating the drug have shown the following benefits:

- There are no necessary dose adjustments in patients with mild to moderate renal or hepatic impairment or on the basis of patient age, sex, and race. Yet its efficacy and safety have not been sufficiently studied in children or adolescents, and it is not approved for pediatric patients; nevertheless, some recent results in acute therapy are promising [91, 96–98].

- Cognitive dysfunction is often present in MDD, and a pro-cognitive effect of an antidepressant is an important issue. Rosenblat et al. reported in a systematic review and meta-analysis that of the antidepressants evaluated (vortioxetine, duloxetine, paroxetine, citalopram, phenelzine, nortriptyline, and sertraline), vortioxetine appeared to have the largest effect size on psycho-motor speed, executive control, and cognitive control [99]. Pehrson et al. reviewed the preclinical data for vortioxetine's effects, at clinically relevant doses, on cognitive function in mechanistic assays and in animal models of depression. The results suggest its neurogenesis and plasticity-promoting effects and that it may have advantages over other antidepressant drugs (regarding its effects on cognitive function) [100].

- Vortioxetine exhibited improvement in overall functioning for patients with MDD and high anxiety symptoms, which often co-occurs; frequently, these patients are difficult to treat, with a higher risk of side effects and suicidal ideation, and register a slower response [93, 97, 101].

- Due to its relatively long half-life, vortioxetine presents a low risk of discontinuation symptoms after rapid cessation of the administration [95, 97].

- Vortioxetine therapy had a low incidence of worrisome changes in vital signs, electrocardiogram parameters, and advantages when talking about treating symptoms of MDD in the elderly [95, 97].

- Unlike most currently antidepressants, drug-associated weight gain and sexual side effects (decreased/loss of libido, delayed ejaculation, erectile dysfunction, anorgasmia, ejaculation disorder, disturbance in sexual arousal, orgasmic sensation decreased/anorgasmia, abnormal orgasm, sexual dysfunction, and ejaculation failure) were not significantly different from placebo [95, 97].

Vortioxetine was well tolerated both in short-term and in long-term studies. Mild to moderate nausea was the most commonly registered side effect, and its frequency was dose related [95, 102]. Due to the lack of well-controlled studies, its administration in pregnancy and lactation is not recommended (**Table 9**) [91].

With more than 50 antidepressant drugs available worldwide (most of them approved for more than 10 years), vortioxetine is the newest agent and needs to determine its place in MDD therapy [97].

System and organ	Manifestations
Gastrointestinal	Nausea, diarrhea, dry mouth, constipation, vomiting, flatulence
Nervous system	Dizziness, abnormal dreams
Skin	Pruritus

Table 9. The most frequent adverse effects of vortioxetine [91, 96, 97, 103].

8. Conclusion

A wide range of antidepressant drugs are available on the market, the most frequent used being the SSRIs, but they do not represent the ideal medication to treat MDD, especially due to the various side effects, that considerably influence the patient's daily life and activity.

Recently introduced in therapy, the four new antidepressants have demonstrated a number of benefits compared to classical medication, represented by faster onset of pharmacodynamic effects, simpler dosage regimen, without necessity of dose adjustment, slight superior efficacy, and less importantly short-term side effects.

Although they have proven efficacy in treating MDD and are being investigated for other possible indications, the risk that these drugs may cause adverse effects following prolonged administration is not fully elucidated. And since most patients undertake antidepressant therapy for several months or years and may suffer from various comorbidities, future detailed clinical trials are needed to establish the pharmaco-toxicological profile of these new antidepressants.

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