Multi-modality as a new pharmacological approach for treatment of depression: the role of vortioxetine

La multimodalità come nuovo approccio nel trattamento della depressione: il ruolo di vortioxetina

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Summary

Recent evidence, such as that from the STAR-D study, have demonstrated that several unmet needs are still present in the treatment of major depression. The "classical" approach adopted to develop new antidepressants drugs, based on selectivity, did not result in increased remission rates in clinical practice, whereas multi-modality represents a new approach to develop novel antidepressants endowed with multiple actions that affect several pharmacological targets. Multimodal antidepressants, developed in the last three years, act through at least two pharmacological modes of action (serotonin reuptake inhibition, agonist/antagonists on neurotransmitter receptors) on at least two or more pharmacologic targets. Vortioxetine is a novel multimodal antidepressant that exerts its antidepressant efficacy in animal models of depression through a combination of two pharmacological modes of action: reuptake inhibition and receptor activity. In vitro studies indicate that vortioxetine is antagonist of 5-HT$_3$, 5-HT$_7$ and 5-HT$_{1D}$ receptors, a partial agonist of 5-HT$_{1B}$ receptors, an agonist of 5-HT$_{1A}$ receptors, and inhibitor of the serotonin transporter. The combination of 5-HT$_{1A}$ agonism with 5-HT$_3$ antagonism can explain the rapid 5-HT cell firing induced by vortioxetine compared to SSRIs such as fluoxetine. Vortioxetine is also able to activate the glutamatergic system in the rat frontal cortex through antagonism at 5-HT$_3$, 5-HT$_7$ receptors. All these pharmacological modes of action can contribute to explain the increased clinical efficacy of vortioxetine in the treatment of cognitive symptoms of depression. Cognitive deficits in depression are often associated with both a suboptimal response to antidepressants and reduced remission rates. Vortioxetine is the first multimodal antidepressant available for the treatment of depression with a specific, positive impact on cognitive symptoms.

Key words

Depression • Serotonin • Multi-modality • Glutamatergic System • Cognitive symptoms • Vortioxetine

Introduction

Depression is one of the most common and invalidating psychiatric disturbances with an incidence of 17-18% in the general population [1 2]. In general, depressive disorders are characterised by significant burden and have enormous impact on patients. They are thus costly not only in terms of healthcare expenses for pharmacological therapy and hospitalizations, but also from social, occupational and personal standpoints. It Italy, at least 1.5 million individuals suffer from depression, while 10% of the population, or about 6 million individuals, have experienced at least one episode of depression during their lifetime [3]. According to the projections of the World Health Organization (WHO), by 2020 depression will be the second leading cause of disability worldwide after cardiovascular disease. Depressive symptoms are frequent in the elderly (> 65 years), and the number of elderly individuals suffering from depression will undoubtedly increase due to the progressive ageing of the general population. Considering gender, women, especially those with an age between 40 and 50 years, are twice as likely to be affected by depression compared to men [4].

Unmet needs in the pharmacological treatment of major depressive disorder

Depression can be diagnosed and treated with pharmacological therapy, despite data from the WHO indicating that less than 25% of affected individuals have access to effective treatments. In the last 60 years, a number of antidepressants belonging to various classes have been developed, which have allowed for improvements in therapy and prognosis of major depressive disorder (MDD). Nonetheless, there are still a number of unmet needs including: slow onset of action, sub-optimal effi-

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cacy, presence of residual symptoms, inefficacy on comorbid cognitive symptoms, treatment of comorbidities, management of elderly patients with depression and problems related to tolerability.

Even if selective serotonin re-uptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally considered as first-line therapy in the treatment of MDD, according to the guidelines of the National Institute for Health and Care Excellence (NICE), about 20–30% of patients with depression do not respond to first-line therapy [7]. Many studies have demonstrated that 60-70% of patients respond to initial antidepressant monotherapy [9], and that more than one-third of patients treated for depression become resistant to therapy even when initial treatment was correctly chosen, administered for an adequate length of time and properly dosed [6]. The correlation between an inadequate response to initial treatment and worsening of prognosis necessitates, therefore, the identification of new agents that provide better clinical response to initial therapy.

Remission, considered as the primary objective of therapy, is defined as a reduction or absence of symptoms for a prolonged period of time [10]. The most common definitions to identify remission in clinical studies are: MADRS ≤ 10, HAM-D17 total score ≤ 7, or CGI-S ≤ 2. Unfortunately, a significant proportion of patients (around 32%) who meet criteria for remission continue to show residual symptoms that are generally more subjective than objective, but which nonetheless have a negative impact on long-term outcomes [8-10]. The presence of residual symptoms is associated with early recurrence and with a reduction in the quality of life and a greater risk of suicide. In the STAR-D study, patients who responded to therapy and who did not experience remission reported 6-7 residual depressive symptoms. The most common included insomnia (94.6%), sadness (70.8%) and decreased concentration (69.6%) [11].

Current treatments help to resolve depressive symptoms in many patients, but in others leave a number of residual symptoms, especially cognitive symptoms [12]. In fact, cognitive symptoms have recently been considered as a critical factor in persistence of disease and in occupational and social disabilities during MDD [13-15]. The association between cognitive deficits, limitations in functioning and major depressive episodes was highlighted in a survey of over 21,000 individuals within the European ESEMeD study [15]. In that study, it was reported a strong association between major depression and cognitive dysfunction, and in particular deficits in concentration and attention. Current antidepressants help to improve mood in many patients, but have limited clinical efficacy in the treatment of cognitive symptoms [12 13 16].

Even if cognitive dysfunction is often unrecognised by the physician, it is nonetheless worrisome for many patients. In a prospective clinical study, more than for other symptoms, patients complained of the presence of at least one cognitive symptom for 94% of the symptomatic period, for 44% of the time during remission and for 66% of the time during three-year follow-up [12].

In patients with MDD who respond to therapy with an SSRI or SNRI, but who are not in remission, cognitive dysfunction persisted in 70% of cases with a reduction in concentration and/or decision-making [25]. In addition, it is known that tricyclic antidepressants (TCA) have a negative effect on cognitive function due to their anticholinergic properties [16]. Taken together, these data show that there is still the need to improve cognitive functioning in patients undergoing treatment with antidepressants.

Another important aspect to consider is that many patients cannot tolerate antidepressant therapy due to adverse effects. In fact, around 50% of patients discontinue antidepressant therapy within 6 months of treatment [17]. Even if adverse events such as nausea and diarrhoea can lead to early discontinuation of treatment, these effects are usually of short duration and resolve after 2-3 weeks. However, long-term adverse effects such as sexual dysfunction, insomnia and weight gain may be present throughout the entire treatment period, and thus have a significant impact on the quality of life and compliance [18]. For persistent or severe adverse effects, guidelines recommend dose reduction, switching to an antidepressant with less propensity for the side effect in question, non-pharmacological treatment, or symptomatic treatment [19]. Nonetheless, the potential benefits of using additional drugs to treat side effects should be evaluated in light of the added risk in terms of safety and tolerability [20]. This approach, however, will considerably increase the costs of therapy.

Treatment-emergent sexual dysfunction (TESD) caused by antidepressants is a problem of considerable importance that can lead to early discontinuation of therapy. The incidence of TESD can be as high as 70% depending on the type and duration of antidepressant therapy [22]. SSRIs are associated with a relatively high propensity to cause sexual dysfunction, and for this reason should be used with caution in patients with pre-existing symptoms related to sexual dysfunction as they could be aggravated by pharmacological treatment [5].

In some cases SSRIs can cause sleep disturbance in patients with depression [23]. Diverse effects have been observed with different types of SSRIs: while fluoxetine and paroxetine are known to delay the REM phase and reduce the duration and efficiency of sleep, sertraline is associated with an increase in the duration and efficiency of sleep and reduced night-time awakenings [23]. Among the SNRIs, venlafaxine increases the time of REM sleep, but can reduce the total duration of sleep [21]. It has been demonstrated that sleep-related adverse

events are the most common cause of discontinuation of treatment with SNRIs in adults [23]. Early relief of insomnia in patients with depression, however, can increase both compliance to treatment and overall functioning, while complete resolution of insomnia significantly improves prognosis in MDD [9].

Weight gain is another common adverse effect that is rare with acute treatment, while it is more frequent during long-term antidepressant therapy. Weight gain is a significant problem in terms of tolerability and is associated with low acceptance to therapy, and consequently with a reduction in long-term compliance [24]. The incidence of weight gain is 18–50% in patients undergoing antidepressant therapy in open-label clinical studies [18]. One of the unmet needs in clinical practice is thus the need to develop new antidepressants that have a better tolerability profile compared to SSRIs and SNRIs, with a lower incidence of side effects including sexual dysfunction and weight gain [37].

New pharmacological targets in treatment of major depression: a new class of multimodal antidepressants

Treatment of MDD during the last 50 years has been mainly based on the monoaminergic hypothesis. However, several lines of evidence have suggested that the monoamine theory of depression is too simplistic to explain a syndrome as complex as depression and the lack of clinical remission in up to 60-70% of patients. The limitations of the monoaminergic hypothesis have emerged from preclinical and clinical studies [26]. Preclinical studies demonstrated that delay between the rapid modification at the synaptic level of biogenic amines in the acute phase and the therapeutic effects seen after at least 3-4 weeks cannot be explained only by the decreased expression of tyrosine hydroxylase and β-adrenergic and serotoninergic (5-HT_{1A}) receptors; it is believed that progressive alterations of specific signalling pathways (CREB, GSK-3beta, AKT/mTOR) related to activation of neurotrophic factors (e.g. brain-derived neurotrophic factor, BDNF) leads to a subsequent impairment [27-29]. These studies suggest that independently of the main 'monoaminergic' activity of many currently used antidepressants, in order to be clinically effective these drugs likely interfere with various signalling pathways that are downstream of monoaminergic receptors. These include BDNF, mTOR and AKT/GSK 3beta signaling pathways, that have driven recent interest in the development of new antidepressants with higher rates of clinical remission [29 30].

Recent evidence, starting with the STAR-D study, has demonstrated that there are still many unmet needs in pharmacological treatment of MDD. An approach based on 'selectivity' focused on a single pharmacological target (e.g. serotonin transporter, SERT) has not led to high rates of remission in controlled or observational studies. Actually, different studies are focused on residual symptoms, which unfortunately prevent the achievement of remission in clinical practice. In this regard, increased attention has also been placed on cognitive symptoms as they are frequently present in many forms of depression that show a sub-optimal response to SSRIs and SNRIs.

Such new evidence implicates that compared to a classic approach adopted to date with selectivity of intervention on individual monoaminergic systems, new multimodal approaches are centred on the development of agents having antidepressant activity with multiple mechanisms of action and that interact with multiple pharmacological targets. According to this scenario multimodal antidepressants can modulate neurotransmitter systems, such as the glutamatergic, dopaminergic and cholinergic, that have not been adequately considered in the treatment of major depression [30 38] (Table I). Multimodal drugs with antidepressant activity developed in the last few years interact with ≥ 2 pharmacological targets (SERT, 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_7) and have more than 2 mechanisms of action (serotonin transporter inhibition, agonism/antagonism of ionotrophic and metabotrophic receptors) [38].

Drug discovery processes in major depression are mainly planned to include multiple mechanisms of action in the same antidepressant in one drug different mechanisms of drugs as observed in combination therapies in clinical practice. Several controlled clinical studies have in fact demonstrated the possibility of increasing response and remission rates by combining SSRIs with noradrenaline and dopamine reuptake inhibitors (NDRI) such as bupropion. However, such advantages were not confirmed in the recent CO-MED study when considering the increased risk of adverse events [38 39].

Drug discovery processes were initially focused on the development of new multimodal antidepressants that could sinergistically potentiate the three monoaminergic systems (5-HT, NA and DA) with triple inhibitors of monoamine reuptake such as amitifadine, even if preregistration clinical studies have still not provided definitive conclusions on the clinical efficacy of these drugs [40].

With the progressive accumulation of new evidence on the involvement of other neurotransmitter systems such as the glutamatergic and cholinergic [41], preclinical research has focused on the development of the first multimodal antidepressant with multiple monoaminergic targets that can interact with ≥ 2 pharmacological targets (SERT, 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_7) and have more than 2 mechanisms of action (serotonin transporter inhibition, agonism/antagonism of receptors) [38] (Table I).

In the development process, this approach has been largely conservative by attempting to maintain the clinical benefits of SERT inhibition but including at the same

time other pharmacological targets such as 5-HT_{1A} receptors in order to reduce the slow onset of action and improve upon the tolerability profile (and in particular sexual dysfunction). Vilazadone was the first effort to develop a multimodal antidepressant whose pharmacodynamic profile includes inhibition of SERT and partial agonism of 5-HT_{1A} (Fig. 1). However, the initial clinical benefits observed in terms of reduction of the onset of clinical action were not confirmed in later studies, and this drug was also found to be associated with gastrointestinal adverse effects [42 43].

Vortioxetine is the latest candidate among multimodal antidepressants. Its pharmacodynamic profile includes not only inhibition of SERT and partial agonism on 5-HT_{1A}, but also antagonism on 5-HT_3 and 5-HT_7 receptors that allows, for the first time, indirect intervention on the glutamatergic system of the prefrontal cortex which to date has not been targeted with currently used antidepressants.

The development of multimodal antidepressants in recent years, and in particular vortioxetine, has been improved in parallel with advances in understanding the neurobiological basis of depression ("the glutamatergic hypothesis of depression"). In addition, classification systems of psychotropic drugs have been revised in the attempt to renew these systems with new evidence in neuroscience, also considering of the wide spectrum of use of psychotropic drugs in clinical practice if referred to their approved indications.

In the last two years, different studies have been carried out at the ECNP (European College of Neuropsychopharmacology) by Joseph Zohar, David Nutt, Guy Goodwin, in collaboration with Stephen Stahl (International College of Neuropsychopharmacology) and the American College of of Neuropsychopharmacology (Pierre Blier and David Kupfer) in order to propose a new classification system based on mechanism of action, and not only on the use of the older nomenclature based on ATC categories and approved indications. For example, antidepressants are effective not only in treatment of major depression, but also in anxiety disorders. At the same time, antipsychotics are used in the treatment of bipolar disorder and not only in psychoses due to their diverse mechanism of action and neurobiological activity profile. The older ATC nomenclature, therefore, does not describe all the potential clinical applications of this class of drugs [44].

In accordance with the new classification (neuroscience-based nomenclature) recently presented at Berlin at the 27th Congress of the European College of Neuropsychopharmacology (18-21 October 2014), every psychotropic drug can be classified according to the following 4 axes:

- Axis 1: Pharmacologic target and mechanism of action. This axis reflects current knowledge of molecular

TABLE I.
Potential advantages of a multimodal approach in the pharmacological treatment of major depression. *I possibili vantaggi dell'approccio multimodale nel trattamento farmacologico della depressione maggiore.*

- Combination of multiple mechanisms of action in a single antidepressant
- Inclusion of new pharmacological targets and interaction with other neurotransmitter systems (e.g., glutamatergic system) in addition to monoaminergic systems (SERT inhibition)
- Possibility to treat residual symptoms such as cognitive symptoms which are frequent depressed patients with a suboptimal response to SSRIs and SNRIs
- Possibility to use antagonistic activity on receptors involved in adverse effects (e.g. 5-HT_3) and consequent improvement of the tolerability profile

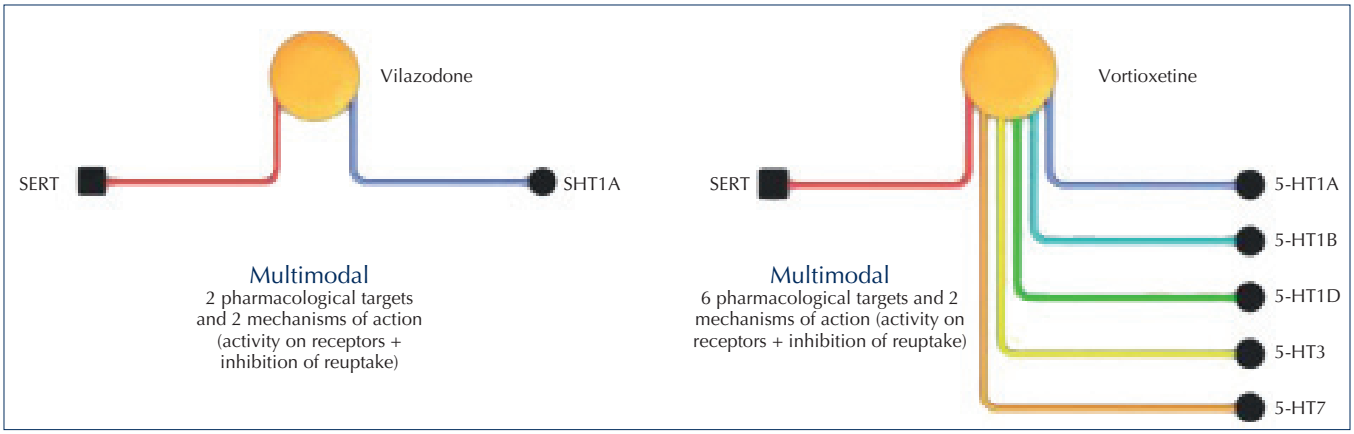


FIGURE 1.
Examples of multimodal antidepressants. *Esempi di antidepressivi multimodali.*

targets and pharmacology and the most accepted hypotheses on its mechanism of action;
- Axis 2: Approved indications. Reports the current therapeutic indications of the drug approved by regulatory authorities (FDA, EMA);
- Axis 3: Efficacy and tolerability. Summarise the evidence on clinical efficacy and most frequent clinical uses, in addition to its tolerability profile and most common adverse effects;
- Axis 4: Neurobiological activity. Describes the main preclinical pharmacology of the drug and primary neurobiological activity on different neurotransmitter systems. In addition, this axis reports, whenever available, relevant clinical data obtained in phase I/II studies.

According to this new nomenclature [45], recent neurobiological understanding of several neuropsychiatric disorders and on the neurobiological activity profile of different psychotropic drugs can be combined in a new system based on mechanism of action that better corresponds to a dimensional approach for a more appropriate clinical use.

In this new scenario, multimodal antidepressants, and in particular vortioxetine, represent a novel opportunity for pharmacological treatment of major depression in light of preclinical and clinical efficacy and possible mechanism of action on multiple psychopathological dimensions (mood, anxiety, cognition) in combination with a good tolerability profile.

Knowledge of the pharmacodynamic profile of vortioxetine thus represents an essential step in understanding the potential advantages of a multimodal approach in pharmacological treatment of depression and the potential use of this drug in clinical practice.

Pharmacodynamic profile of vortioxetine: from development to new pharmacologcal targets

Vortioxetine is an example of a multimodal antidepressant that, in addition to classic inhibition of SERT, is also a full agonist of 5-HT_{1A} receptors, partial agonist of 5-HT_{1B} receptors and an antagonist of 5-HT_{1D}, 5-HT3 and 5-HT_7 receptors (Fig. 1). The drug discovery of vortioxetine is a good example of innovation and serendipity. The initial objective in the development of vortioxetine was to develop a lead compound that combined SERT inhibition with: 1) 5-HT_{1A} agonism to reduce the slow onset of clinical action and minimise side effects related to sexual dysfunction; 2) antagonism of 5-HT_3 to reduce nausea, a frequent side effect with SSRIs during the first few weeks of treatment [46 47].

During development of vortioxetine it was observed that 5-HT_3 antagonism led to further potentiation of the serotoninergic system (extracellular accumulation of 5-HT) in addition to that produced by inhibition of SERT [48]. Moreover, in the initial design of the molecule 5-HT_{1B} agonism was not anticipated, which was later revealed to be important for potentiating the SSRI action of vortioxetine in animal models of depression, and especially antagonism of 5-HT_7 receptors that no other antidepressant had. This rendered vortioxetine unique compared with other antidepressants as a possible positive, indirect modulator of the glutamatergic system [46].

Following the drug discovery process, the pharmacodynamic profile of vortioxetine was characterised by an elevated potential to inhibit SERT with an affinity similar to escitalopram (1.6 nM *vs* 10 nM), along with intrinsic full agonist activity for 5-HT_{1A} receptors, partial agonist activity for 5-HT_{1B} receptors and antagonist activity for 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors (Table 2, Figure 2) [46 47 49].

If the pharmacodynamic profile and functional activity of vortioxetine is compared in rats and humans it can be observed that vortioxetine has affinity binding values that are similar for the different types of receptors with the exception of 5-HT_{1A} and 5-HT_7 where the affinity is higher in humans (Table II). Preclinical pharmacological studies have considered this difference relevant and adopted a range of doses starting with 0.5 mg/kg, a dose that corresponds, after an acute treatment in rats, to an occupation of 5-HT_3 and 5-HT_{1D} receptors and 50% of SERT, up to doses of 5-10 mg/kg in which vortioxetine fully occupies the 5-HT_{1B}, 5-HT_{1A} and 5-HT_7 receptors [46].

To describe the pharmacodynamic profile of vortioxetine it is necessary to consider the contribution of serotonergic receptors, and in particular 5-HT_{1A}, 5-HT_3 and 5-HT_7, in order to explain the broad spectrum of efficacy of the drug not only in classic animal models of depression, but also in newer preclinical models in which currently-available SSRIs are not efficacious [46]. 5-HT_{1A} receptors have an important role in clinical response to antidepressants in treatment of major depression [50]. As already mentioned, preclinical studies have demonstrated that the difference in the onset of therapeutic action and the rapid modification at the synaptic level of biogenic amines in the acute phase observed after 3-4 weeks cannot be explained by down-regulation of 5-HT_{1A} receptors alone, but with the progressive alteration of other specific signaling pathways (CREB, GSK-3beta, AKT/mTOR), the increased release of neurotrophic factors (e.g. BDNF) and the consequent effects on synaptic plasticity [47 51 52].

5-HT_{1A} receptors are a subgroup of receptors localised at the somatodendritic level of serotonergic neurons that originate at the level of the raphe nuclei as well as at the presynaptic level in the terminations of serotonergic neurons at different areas of the CNS, such as the hippocampus and prefrontal cortex. At the somatodendritic level, 5-HT_{1A} receptors inhibit firing of serotonergic neurons;

TABLE II.
Multimodal activity of vortioxetine: differences in affinity between humans and rats. *L'attività multimodale di vortioxetina: le differenze di affinità tra uomo e ratto.*

	Affinity (nM)	
Receptor	**Rat**	**Human**
5-HT$_3$	1.1	3.7
5-HT$_7$	190	19
5-HT$_{1A}$	230	15
5-HT$_{1B}$	16	33
5-HT$_{1D}$	3,7	54
SERT	8,6	1,6

desensitization and especially down-regulation of 5-HT$_{1A}$ receptors is crucial for the clinical efficacy of antidepressants [50]. In the first phase of treatment with SSRI antidepressants, 5-HT$_{1A}$ receptors are stimulated by elevated levels of 5-HT with consequent inhibition of firing and the possible presence of anxiety symptoms. In succession, 5-HT$_{1A}$ receptors undergo progressive desensitisation and especially down-regulation with consequent recovery and a successive increase in firing of serotonergic neurons. Vortioxetine, due to the combination of full agonism of 5-HT$_{1A}$ and antagonism of 5-HT$_3$ together with classic SERT inhibition, leads to rapid desensitization of 5-HT$_{1A}$ receptors with rapid activation of the serotonergic system compared to SSRIs such as fluoxetine (24 h *vs* 7 days) [46]

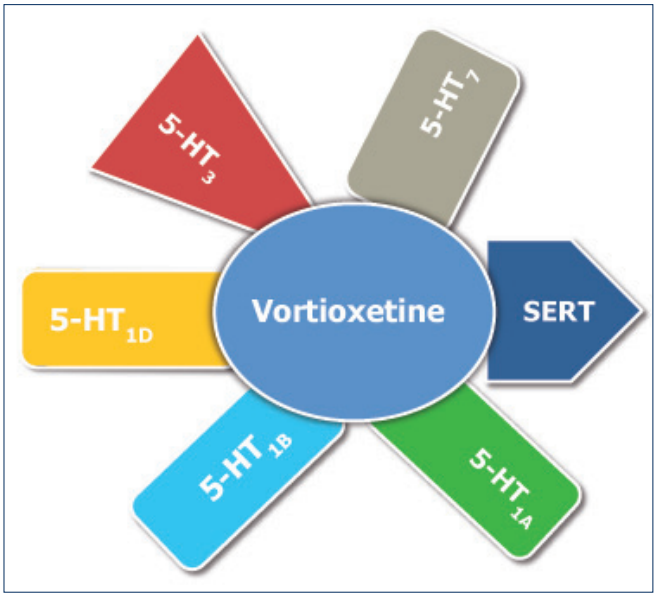
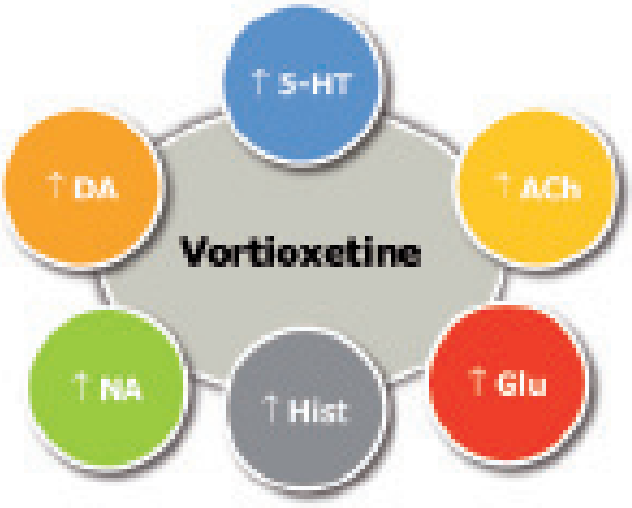


FIGURE 2.
Pharmacodynamic profile of vortioxetine. *Profilo farmacodinamico di vortioxetina.*

[53 54]. It has been hypothesize that the antagonism on presynaptic 5-HT$_{1D}$ receptors, included in the mechanism of action of vortioxetine, could contribute to the potentiation of the serotonergic system since it is known that selective antagonists of 5-HT$_{1D}$ receptors potentiate the increase in extracellular levels of 5-HT induced by SSRIs [55].
It has been demonstrated that the effects of vortioxetine on serotonergic neurons of the raphe depend significantly on antagonism of 5-HT$_3$ receptors [46]. It is already well-known that the combination of 5-HT$_3$ receptor antagonists with SSRIs potentiates the extracellular increase in serotonin in the prefrontal cortex and ventral hippocampus compared with a single treatment with SSRI [48]. It has also been demonstrated in rats that agonists of 5-HT$_3$ receptors such as SR57227 prevent the rapid reactivation of the serotonergic system observed after a long-term administration of vortioxetine at a dose of 5 mg/kg [53]. These pharmacological effects of vortioxetine observed in animal models could lead to a better tolerability profile during the first week of treatment with a reduction in anxiety symptoms associated with inhibition of the serotonergic system induced by SSRIs during the first days of treatment.
A specific feature of the pharmacodynamic profile of vortioxetine is the ability to indirectly potentiate the activity of other neurotransmitter systems involved in the pathogenesis of major depression such as the noradrenergic, dopaminergic, cholinergic, and in particular the glutamatergic system; a major pharmacological target recently studied for the treatment of depression (Fig. 3).
Vortioxetine significantly increases the extracellular levels of noradrenaline (NA) in the prefrontal medial cortex and ventral hippocampus following acute or chronic administration in rats [54]. It is interesting to note that vortioxetine is not associated with a significant inhibition of the noradrenaline transporter (NAT) at either the level of the central or peripheral nervous system; it does not increase the peripheral levels of NA as observed with SNRI antidepressants, which through NET inhibition, can favour the onset of adverse effects such as tachycardia and an increase in arterial blood pressure [57 58]. Recent evidence suggests that vortioxetine indirectly potentiates the NA system at the medial prefrontal cortex and ventral hippocampus due to antagonism of 5-HT$_3$ combined with agonism of 5-HT$_{1A}$ receptors [46]. Antagonism on 5-HT$_3$ receptors leads to a reduced release NA in the locus coeruleus along with a reduced activation of inhibitory presynaptic α_2 receptors and the following increase in firing of noradrenergic neurons starting from the locus coeruleus with a concomitant release of NA in the prefrontal cortex and hippocampus. The agonism on 5-HT$_{1A}$ receptors contributes to potentiation of this effect as it leads to an increase in the extracellular levels of NA in the same areas [46 58].

Vortioxetine, due to its agonist activity on 5-HT_{1A} receptors, also leads to an increase in the extracellular levels of dopamine (DA) in the medial prefrontal cortex at a dose of 5 mg/kg, while it does not influence the activity of the mesolimbic dopaminergic system or the release of DA in the nucleus accumbens [46 54]. Moreover, vortioxetine, in addition to its activity on monoaminergic systems, increases the release of acetylcholine and histamine in the medial prefrontal cortex (Fig. 3).

FIGURE 3.
Direct and indirect effects of vortioxetine on neurotransmitter systems. *Effetti diretti e indiretti di vortioxetina sui sistemi neurotrasmettitoriali.*



SERT: serotonin transporter; 5-HT: serotonin; ACh: acetylcholine; Hist: histamine; NA: noradrenaline; DA: dopamine.

Interaction between the serotonergic and glutamatergic systems: the specific role of vortioxetine

The glutamatergic system plays an essential role in the pathophysiology of major depression and in the pathogenesis of cognitive symptoms in depression [59 60]. The glutamatergic system is considered a relevant pharmacological target for the development of new antidepressants with a better pharmacodynamic profile, especially in the management of treatment-resistant depression [30 59].
In major depression, it has been demonstrated a dysfunction of the glutamatergic system consisting of hyperactivation of ionotropic NMDA receptors for glutamate with an increased release of glutamate correlated with acute stress and possible neurodegenerative phenomena in the prefrontal cortex and hippocampus [28 29]. It has also been shown that first and second generation antidepressants can reduce the release of glutamate, especially after acute stress, and that they can reduce glutamatergic transmission at the levels of NMDA receptors, potentiating AMPA receptors [28].
The discovery of the rapid antidepressant action of ketamine, a non-competitive antagonist of NMDA receptors, in patients with treatment-resistant depression has opened new avenues for the identification of new pharmacological targets and developing new antidepressants that can directly or indirectly modulate the glutamatergic system [61].
Ketamine is an effective drug for therapy of treatment-resistant depression, although it is associated with psychotomimetic effects (hallucinations and perception disorders) and has a high potential for abuse as highlighted by several studies [29]. Moreover, it has been demonstrated that abuse of ketamine may also lead to comprised cognitive function and alteration in thought content [29]. Considering these aspects, it is clear that ketamine cannot be readily used in clinical practice due to issues regarding tolerability and safety. It is thus necessary to develop new antidepressants with serotoninergic action that can also indirectly modulate the glutamatergic system [61].
The serotonergic system influences the glutamatergic system through 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 receptors. Ketamine loses its antidepressant efficacy in animal models following depletion of serotonin, which suggests that the serotonergic system has an essential role in modulation of the glutamatergic system. Multimodal antidepressants such as vortioxetine can modulate the glutamatergic system through interaction with serotonergic receptors including 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 which can regulate the neurobiological effects of the serotonergic system on the glutamatergic system.
Recent studies suggest that vortioxetine, through antagonism of 5-HT_3 and 5-HT_7 receptors, exerts a positive modulation on the glutamatergic system in the prefrontal cortex. This action may lead to an increase in clinical efficacy when treating residual symptoms, such as cognitive symptoms, which are often present in patients with suboptimal or inadequate response to antidepressants finally preventing the achievement of complete remission in clinical practice [61 62]. Similar to ketamine, vortioxetine also selectively activates the Akt/mTOR pathway, unlike SSRIs which inactivate it. Of interest, the Akt/mTOR pathway has an essential role in mediating the synaptic and neurotropic effects of ketamine [29 63]. Moreover, it has been hypothesized that vortioxetine, through antagonism of 5-HT_3 receptors expressed on dendrites of GABAergic neurons, reduces the inhibition exerted by 5-HT_3 on pyramidal glutamatergic neurons in the prefrontal cortex and at the same time inhibits the activity of GABAergic neurons at the level of CA1 region of the hippocampus [61].
In addition, prolonged antagonism on 5-HT_3 receptors leads to the induction of long-term potentiation (LTP), one

of the most important molecular and cellular phenomena underlying learning and memory, as recently observed with vortioxetine in ex vivo hippocampal studies in rats [64]. These studies showed for the first time that vortioxetine prevents the increase of inhibitory postsynaptic currents induced by serotonin at the level of pyramidal cells in the CA1 region of the hippocampus and enhances LTP, events that are not modified by treatment with SSRIs such as escitalopram [64]. Augmentation of LTP by vortioxetine also stimulated neurogenic processes in the subgranular zone of the dentate gyrus in mice within 14 days of treatment in contrast to that observed with fluoxetine, which leads to proliferation and differentiation of neural precursors after only 21 days of treatment [65]. It is interesting to note that vortioxetine, after 14 days at a dose of 20 mg/kg, also leads to significant increases of dendrites lenght and dendritic connections, which are likely related to the selective activation of the AKT/mTOR pathway.

Finally, vortioxetine enhances the glutamatergic system at the level of the prefrontal cortex and hippocampus through antagonism on 5-HT$_7$ receptors [61]. 5-HT$_7$ receptors are located on the soma and the presynaptic terminals of glutamatergic pyramidal neurons that project from the prefrontal cortex to the raphe nuclei, from which serotonergic neurons originate. Moreover, 5-HT$_7$ receptors are expressed on GABAergic interneurons at the level of the prefrontal cortex and hippocampus. The antagonism on 5-HT$_7$ receptors by vortioxetine directly on glutamatergic neurons of the prefrontal cortex leads to an enhancement of glutamatergic transmission towards the raphe nuclei with a subsequent activation of serotonergic neurons [61].

In animal models, it is known that 5-HT$_7$ antagonists enhance the response to SSRIs and improve memory and executive functioning in models of cognitive dysfunction induced by the administration of competitive antagonists of NMDA receptor such as MK-801 or addictive substances such as phencyclidine [61 66]. It is interesting to note that in these animal models synergistic efficacy was seen by combining SSRIs with selective 5-HT$_7$ antagonists [67]. Importantly, vortioxetine combines both of these pharmacodynamic properties in the same molecule.

Taken together, the effects of vortioxetine on the glutamatergic system, neurogenic processes and synaptic plasticity can explain its clinical efficacy in both animal models of depression and in cognitive dysfunction in depressed patients with cognitive deficits [62] or suboptimal response to SSRIs [68]. In particular, the positive modulation of the glutamatergic system in the prefrontal cortex, through antagonism of 5-HT$_3$ and 5-HT$_7$ receptors, is associated with an increased clinical efficacy compared to SSRIs in the treatment of residual symptoms such as cognitive symptoms that prevent the achievement of functional remission in clinical practice.

Preclinical efficacy of vortioxetine in animal models of depression

In recent years, vortioxetine has been extensively studied in animal models of depression, and has shown efficacy as an antidepressant in rodents in the range of 1-10 mg/kg [46]. This has been demonstrated following acute administration in classic behavioural tests such as the forced swim test (both in mice and in Flinders sensitive line rats), the rat social interaction test and the novelty-suppressed feeding test [65]. The efficacy of vortioxetine in these animal models is based on the monoamine hypothesis even after 14-21 days of treatment [65], and is also efficacious in animal models of depression in which SSRIs are ineffective. In particular, it has been demonstrated that vortioxetine is effective in C57 mice that do not respond to SSRIs [69] and in an animal model based on the GABAergic hypothesis of depression known as progesterone withdrawal. In this model, the abrupt discontinuation of progesterone administration in the rat following a long-term treatment (21 days) leads to the onset of anxiety, irritability and a depressive phenotype with anhedonia and social withdrawal. The administration of vortioxetine has an antidepressant effect as measured by the forced swim test, in contrast to that observed with fluoxetine or duloxetine in this model [70 71].

Due to its multimodal action and its ability to interact with multiple targets, vortioxetine has an antidepressant effect in animal models after a sub-chronic treatment at a dose of 5 mg/kg, a dose that is associated with only a partial occupation of SERT (40%). It can be hypothesize, in fact, that agonism on 5-HT$_{1A}$ receptors in combination with antagonism on 5-HT$_3$ receptors, is essential for increasing the efficacy of vortioxetine compared with SSRIs in animal models where SSRIs and SNRIs are ineffective.

In recent years, research in psychopharmacology has focused on improving the translational value of animal studies with the aim of developing a model with an increased predictive value [30]. The main problem, in fact, is that of reproducing, within the limits of the large differences between rodents and humans, behavioural phenotypes that have the same neurobiological basis of symptoms such as cognitive deficits (attention, memory and executive functioning) that still represent the most relevant unmet needs in the pharmacological treatment of depression.

Animal models of cognitive dysfunction: the unique mechanism of action of vortioxetine

Vortioxetine is the first example of an antidepressant that has been widely studied not only in animal models of depression, but also in all the newer models of cognitive dysfunction (and in particular attention, memory and executive functioning) where SSRIs such as fluoxetine and

escitalopram are ineffective [72]. It is interesting to note that the increased spectrum of preclinical efficacy of vortioxetine in animal models of depression was also seen in terms of clinical efficacy in treatment of cognitive deficits in MDD [62]. Among the main mechanisms involved in this effect, it is believed that enhancement of the cholinergic and glutamatergic systems in the hippocampus and activation of the dopaminergic system in the prefrontal cortex arising from the multimodal action of vortioxetine are most relevant since these neurotransmitters have a role in cognitive functions such as attention, memory and executive functioning [46 72]. Study of EEG patterns in rodents has confirmed that there are relevant differences between vortioxetine and second-generation antidepressants (SSRIs and SNRIs) in terms of general neurobiological effects, and in particular on the state of vigilance [72]. Quantitative analysis of the EEG in the prefrontal cortex in rodents has a good translational value and is a validated method to predict EEG patterns in man [72]. It is known, in fact, that the activity on theta and gamma waves is directly correlated with memory encoding and retrieval, whereas alpha and gamma waves are mostly associated with attention [73]. A close correlation between the antidepressant effects in the quantitative analysis of EEG at the prefrontal cortex and the effects of these drugs on cognitive function has been demonstrated [72]. In particular, it has been observed in rats that vortioxetine, even at a dose of 5 mg/kg administered in acute (corresponding to 80% occupation of SERT), is associated with a completely different EEG pattern than either escitalopram (2 mg/kg) or duloxetine (10 mg/kg) administered at doses that lead to 80% occupation of SERT (and thus equivalent doses in preclinical terms) [72]. Vortioxetine increases the activity of alpha, theta and gamma by 25-60%, in contrast to escitalopram and duloxetine which reduce their activity. The authors of that study also demonstrated that the effects of vortioxetine are mediated by the 5-HT_{1A}, 5-HT_3 and 5-HT_7 receptors [73]. These data, together with that of Dale et al. [64] on the enhancement of LTP, can explain the effects of vortioxetine in animal models of cognitive dysfunction [72].

In fact, vortioxetine has been demonstrated to potentiate processes of acquisition and retention of memory (including visuospatial) in many rodent models [46 72]. In particular, vortioxetine reverts memory deficits in the rat induced by serotonin depletion following administration of selective inhibitors of tryptophan hydroxylase [74 75]. The effects of vortioxetine have been observed in the novel object recognition test even at low doses (0.1 mg/kg) in which 80% of 5-HT_3 receptors are blocked. In the same animal model, the authors demonstrated that the pro-cognitive action of vortioxetine is related not only to antagonism of 5-HT_3 receptors, but also to agonism of 5-HT_{1A} receptors [74]. In the same animal model, SSRIs such as escitalopram and SNRIs such as duloxetine are not able to 'correct' memory deficits induced by serotonin depletion [75]. Therefore, occupation of SERT does not seem to be relevant in 'rescuing' cognitive deficits in animal models, and the multimodal activity of vortioxetine acquires provides an added value when considering its pharmacodynamic profile [46 75]. Moreover, in adult rats, vortioxetine is associated with recovery of learning that has been compromised by treatment with selective inhibitors of tryptophan hydroxylase or exposition to chronic stress (i.e. cold) [76]. Lastly, administration of vortioxetine for 4 weeks in older C57BL/6 mice (12 months) leads to improvements in visuospatial memory, whereas fluoxetine, even at high doses, is ineffective in the same model [69].

Vortioxetine has also been demonstrated to be effective in a preclinical rat model of dysfunction of attention and executive function induced by subchronic administration of phencyclidine (PCP, 5 mg/kg for 7 days) [46]. This is an important model for validation of the hypothesis that the glutamatergic action of vortioxetine is relevant to its action. In the PCP model, in fact, the glutamatergic system is compromised at the level of the prefrontal cortex. Vortioxetine is able to revert these effects, resulting in improvement in tests of attention and executive function even at a dose of 3 mg/kg administered either chronically or acutely [46 77].

Overall these data (Table III) can explain why the broad spectrum of preclinical efficacy seen with vortioxetine in animal models of cognitive dysfunction are confirmed in controlled clinical studies where vortioxetine has been shown to be effective in treatment of cognitive deficits in major depression [62].

Pharmacokinetic profile of vortioxetine

Pharmacokinetic studies in healthy volunteers in preregistration studies showed that vortioxetine has a linear pharmacokinetics over a wide dose range from 2.5-60 mg/day following a single administration [78]. Vortioxetine has a half-life of 66 hours and steady-state plasma levels are reached in about 2 weeks (12-14 days). The absolute bioavailability of vortioxetine is 75% after oral administration and its absorption is not influenced by food. In addition, vortioxetine shows an high level of plasma proteins binding (98%; Table IV) [79].

The main pharmacokinetic parameters of vortioxetine are a T_{max} of 7-8 hours (time needed to reach a maximal plasma concentration after a single administration) and a C_{max} of 9 ng/ml after a dose of 5 mg/day and 33 ng/ml after a dose of 20 mg/day (Table IV). The starting dose is 10 mg/day in a single administration with the possibility to increase the dose to 20 mg/day after one week of treatment, or reduce it to 5 mg/day depending on the individual response [79].

Vortioxetine is metabolized by oxidation via multiple CYP450 isozymes (CYP2D6, 3A4/5, 2C19, 2C9 and 2B6) and the following conjugation with glucuronic acid [80]. CYP2D6 is the major isoenzyme involved in the phase I metabolism of vortioxetine [81]. Plasma concentrations of vortioxetine are about twice in CYP2D6 poor metabolizers compared to extensive metabolizers [79]. The maximum dose in poor metabolizers is 10 mg/day. The metabolites of vortioxetine [main metabolite 3-methyl-4-(2-piperazine-1-yl-phenylsulphanyl)-benzoic acid] do not have antidepressant activity, do not cross the blood-brain barrier and are thus not pharmacologically relevant [46]. No relevant differences have been observed in the main pharmacokinetic parameters in relation to gender or in the presence of reduced hepatic or renal function [79].

It is important to underline that vortioxetine, in contrast to several SSRIs (fluoxetine, paroxetine, fluvoxamine) and SNRIs (duloxetine), does not inhibit several isoenzymes of CYP450 (CYP2D6, 3A4/5, 2C19, 2C9) and thus does not have any clinically relevant drug interactions.

Polypharmacy is a common and frequent practice in psychiatry due to treatment of comorbidities or as add-on therapy. The availability of different classes of drugs has also increased the probability of pharmacodynamic and pharmacokinetic interactions with consequent risk of morbidity and mortality, especially in the elderly population. Detailed knowledge of clinically-significant pharmacological interactions is therefore needed on the basis of the available evidence [82]. SSRIs an heterogeneous class of antidepressants with substantial differences in pharmacodynamics and pharmacokinetics. Some SSRIs such as fluoxetine, paroxetine and fluvoxamine can modify the plasma concentrations of other psychotropic drugs by inhibiting CYP450 isoenzymes, thus causing clinically-relevant pharmacological interactions [82].

According to this scenario, vortioxetine has an advantage compared to SSRIs because it does not modify the activity of CYP450 isoenzymes, and thus does not cause clinically-relevant pharmacological interactions [60]. It is nonetheless important to specify that inhibitors of CYP2D6 such as bupropion or inhibitors of CYP3A4 such as fluconazole and ketoconazole can increase the AUC and C_{max} of vortioxetine (respectively +128% and 114% for bupropion, +46% and +15% for fluconazole, +30% and +26% for ketoconazole) [60]. However, these interactions are not clinically relevant considering the broad therapeutic index of vortioxetine, even if in such cases appropriate dose reduction of vortioxetine should be considered in case of interaction with inducers of CYP3A4 such as rifampicin that reduce the AUC and C_{max} (respectively -73% and -51%); in this case a dose increase of vortioxetine can be considered [81].

Overall these data suggest that vortioxetine has a favourable pharmacokinetic and tolerability profile char-

TABLE III.
Summary of evidence in preclinical studies [25 41]. *Sommario delle evidenze negli studi di farmacologia preclinica [25 41].*

Target	Action	Results in preclinical models
5-HT_3	Antagonism	Increase in the effects of SSRIs / SNRIs Enhancement of extracellular increase of 5-HT in the medial prefrontal cortex and ventral hippocampus compared to monotherapy with SSRI in rats Increase in extracellular levels of noradrenaline in the medial prefrontal cortex and ventral hippocampus in rats Positive modulation of the glutamatergic system in the prefrontal cortex Inhibition of GABAergic neurons at CA1 in the hippocampus of rats and augmentation of LTP Procognitive effects in rats depleted of 5-HT and improvements in memory and executive function
5-HT_7	Antagonism	Antidepressant and anxiolytic properties Potentiation of the antidepressant effects of SSRIs in animal models of depression Positive modulation of the glutamatergic system in the prefrontal cortex Improvement of memory and executive function in animal models of cognitive dysfunction
5-HT_{1D}	Antagonism	Enhancement of the extracellular increase of 5-HT compared to monotherapy with SSRIs
5-HT_{1B}	Partial agonism	Potentiation of the antidepressant effects of SSRIs in animal models of depression
5-HT_{1A}	Agonism	Antidepressant and anxiolytic properties Acceleration of desensitization of somatodendritic 5-HT_{1A} autoreceptors with a more rapid reactivation of the serotonergic system in animal models Increase in extracellular levels of dopamine and noradrenaline in the medial prefrontal cortex Procognitive effects in rats following depletion of 5-HT
SERT	Inhibition	Antidepressant and anxiolytic properties in animal models

TABLE IV.
Pharmacokinetic profile of vortioxetine. *Profilo farmacocinetico di vortioxetina*.

Parameter	Vortioxetine
Oral bioavailability	75%
Half-life	66h
T_{max}	7-8h
C_{max}	9 ng/ml (5 mg/die); 18 ng/ml (10 mg/die) 33 ng/ml (20 mg/die)
Plasma binding	98%
Metabolism	*CYP2D6*, 3A4/5, 2C19, 2C9 and 2B6
Drug interactions	*Vortioxetine does not inhibit CYP450 isozymes and does not have any pharmacologically relevant drug interactions* Does reduction is needed in case of co-administration with bupropion, fluconazole or ketoconazole, while dose increase may be needed in case of co-administration with rifampicin
Starting dose	10 mg/die
Dose adjustments	Can be increased (up to 20 mg/day) or decreased (5 mg/day) after 1 week
Administration	Once daily

acterized by the absence of sexual adverse events and weight gain [79].

Conclusions

Multimodal antidepressants are a new psychopharmacological tool for the treatment of major depression. This new pharmacological class includes agents with antidepressant activity which have multiple mechanisms of action. These drugs interact with multiple pharmacological targets thereby modulating several neurotransmitter systems that have not been addressed until now in treatment of major depression, such as glutamatergic, dopaminergic and cholinergic systems. Vortioxetine is an example of a multimodal antidepressant that, in addition to classic inhibition of SERT, also acts as a full agonist on 5-HT_{1A} receptors, partial agonist on 5-HT_{1B} receptors and antagonist on 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors.
All the evidence presented in this review that vortioxetine has a broad spectrum of efficacy not only in classic animal models of depression, but also in all the newer animal models of cognitive dysfunction (especially memory and executive function). In particular, vortioxetine is the first example of a multimodal antidepressant that, due to its multiple mechanisms of action in addition to SERT inhibition, has been shown to be effective in all animal models of depression and cognitive dysfunction where SSRIs such as fluoxetine and escitalopram and SNRIs such as duloxetine are ineffective [46]. The multiple pharmacological effects of vortioxetine associated with a multimodal approach provide a broad profile of clinical efficacy on multiple psychopathological dimensions (mood, anxiety, cognition) together with a good tolerability profile charcterized by the absence of sexual adverse effects without a significant weight gain [46 79].

Conflict of interests
Filippo Caraci, in relation to the issues treated in the last three years, was a consultant and/or speaker at symposia organized by Lundbeck, Eli-Lilly, Otuska, Grunenthal, Janssen.
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