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Introduction

Generalized anxiety disorder (GAD) is a common mental disorder marked by persistent, distressing, and excessive anxiety and worry (apprehensive expectation) about several events/situations/activities (i.e. work, school performance, etc.) [1]. The intensity, duration, and frequency of the anxiety and worry are out of control and may be associated with irritability, muscle tension, sleep disturbance (i.e. restlessness, staying asleep, etc.), fatigue, difficult concentration, and restlessness [1]. Subjects affected with GAD may have a significant impairment in work, social and family functioning, as well as a worsening in health-related quality of life [2,3]. GAD usually has a chronic course [4]. The 12-month prevalence of GAD ranges from 0.4% to 3.6%, depending on the countries [1]. Lifetime prevalence of GAD is approximately 6% [5]. GAD is highly associated with comorbid psychiatric conditions, particularly with major depressive disorder (MDD), with a rate ranging 28–55% [6,7]. Given the aforementioned findings, proper and effective treatment of GAD is fundamental [8].

According to the most recent guidelines, the first-line pharmacological strategies in the treatment of GAD comprise selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [9,10]. Promising results have also been obtained with pregabalin and quetiapine [10]. Further useful alternative treatments include buspirone, benzodiazepines, and hydroxyzine [11]. However, most patients affected with GAD do not receive an adequate response to initial treatment with an SSRI/SNRI, with differences in the response rate between SSRI/SNRI and placebo ranging from 15% to 20% [12].

Vortioxetine (LU-AA21004; 1-[2-(2,4-dimethylphenyl-sulfonyl)-phenyl]-piperazine; Brintellix®; VRX) is a multimodal-acting antidepressant agent, recently identified in a designed multiple ligands program by H. Lundbeck A/S and co-marketed by Lundbeck® and Takeda® [13,14]. In September 2013, VRX was approved in North America by the US FDA for the once-daily treatment of adults with MDD [14,15]. Recently, it was also approved in Europe by the European Medicines...
Agency for the same indication [16]. VRX is in phase III development for the treatment of GAD and in phase II development for anxiety and depressive disorders in children and adolescents (NCT01491035), as well as attention-deficit hyperactivity disorder. A further phase IV, open-label study is still evaluating its efficacy and safety for panic disorder (PD; NCT02395510).

Chemistry

It belongs to the chemical class of the bisarylsulfanyl amines. It is structurally related to citalopram, ondansetron, and buspirone [17]. Figure 1 shows the chemical structure of VRX.

Pharmacodynamics

The structure–activity relationship studies, made by in vitro binding affinity assays, revealed the substantial activity as human serotonin (5-HT) transporter (SERT) inhibitor by VRX (Ki = 1.6 nmol/l in human receptors), as well as a discrete action as norepinephrine transporter (NET) blocker (Ki = 113 nmol/l) [18,19]. Its SERT occupancy rates range from 50% at 5 mg/day, 53–65% at 10 mg/day, to >80% at 20 mg/day [20,21]. Furthermore, VRX has been demonstrated to act as a partial agonist (with near full agonist activity) at 5-HT1A receptors (Ki = 15 nmol/l), partial agonist at 5-HT1B (Ki = 33 nmol/l), antagonist at 5-HT1D (Ki = 54 nmol/l), antagonist at 5-HT3A (Ki = 3.7 nmol/l), antagonist at 5-HT7 (Ki = 19 nmol/l), as well as to bind with high affinity, but not obvious in vivo pharmacology, at noradrenergic β1 receptors (Ki = 46 nmol/l) [22–25]. These pharmacological properties induced discoverers to define VRX as a new serotonergic multimodal agent with pleiotropic activity on multiple serotonin-related neurotransmissions and thereby with potential benefits in the treatment of MDD. Indeed, several studies have pointed out the role of specific serotonin receptors modulation in the management of core depressive symptoms. In particular, attention has been progressively focusing on 5-HT1A receptors. These subclasses of seven-transmembrane passage serotonin receptors are ubiquitously distributed in the brain, with scarce differences among species (i.e. from rat to human) [26–29]. 5-HT1A receptors may be both presynaptically and postsynaptically localized. Particularly, 5-HT1A presynaptic autoreceptors are mainly located on serotonergic neurons of the raphe nuclei [30], whereas postsynaptic 5-HT1A receptors are principally distributed in the cortex, as well as in the hippocampus, septum, amygdala, and hypothalamus [26,27]. Both types of 5-HT1A receptors act as G-protein-coupled receptors, whose principal effect is the modulation of inward rectifier K+ channels through cAMP and phospholipase C, thereby causing the final reduction of firing by neurons involved [31,32]. The potential antidepressant effects of 5-HT1A modulation were already suggested in early studies, in which some authors reported that the add-on of pindolol (a β-adrenergic receptors blocking agent, with partial agonist properties at 5-HT1A used to treat hypertension) to paroxetine could accelerate the improvement of depressed patients treated with the serotonin reuptake inhibitor [33,34]. Pindolol was previously known to exert antagonistic activity at 5-HT1A receptors. However, successive studies have demonstrated that actually, pindolol may possess agonist-like activity at somatodendritic 5-HT1A receptors, with weak antagonistic properties [35]. Successive studies determined and confirmed the partial agonist properties of pindolol but somewhat stated that other 5-HT receptors should be involved in the antidepressant-potentiation effects by this drug [36]. Recent reports also demonstrated the involvement of 5-HT1A receptors in anxiety-like behaviors and in the susceptibility to anxiety disorders [37]. Moreover, drugs with antagonistic actions at 5-HT1A receptors have been reported to display anxiolytic effects [38].

Its partial agonist activity at 5-HT1B receptors may exert effects in modulating stress sensitivity, mood, anxiety, and aggression by inhibiting the release of 5-HT, NE, GABA, acetylcholine, and glutamate [39]. In fact, 5-HT1B receptors have also been associated to both anxiety and depression in animals as well as in human studies [40,41]. These are G-coupled receptors principally localized on the serotonergic terminals of dorsal raphe nucleus efferent fibers, acting as autoreceptors that respond to serotonin extracellular elevation by feedback inhibiting further release and synthesis and enhancing serotonin reuptake [42–44]. Animal models of learned helplessness induced by stress have been reported to express high levels of 5-HT1B receptors in the dorsal raphe nucleus [45], as well as the viral-induced overexpression of 5-HT1B receptors in the same nucleus may induce anxiety behaviors [46]. However, other studies revealed a substantial increase in 5-HT1B receptors percentage in the dorsal raphe nucleus in animal models of stress resistance [47], thus defining a complex role of these receptors in anxiety. SSRIs have been demonstrated to reduce 5-HT1B expression in the dorsal raphe nucleus in a time- and dose-dependent manner [48]. Recent studies, moreover, demonstrated that 5-HT1B agonists may counteract the onset of anxiogenic behaviors in animals exposed to fear contexts [49]. By contrast, anxiogenic responses may be induced in animals by selectively injecting 5-HT1A agonist drugs in the medial prefrontal cortex, a brain region crucially involved in processing emotional behaviors [50]. 5-HT1A antagonists may also display anxiolytic effects when systemically administered [51]. Given the composite action of 5-HT1B receptors on anxiety behaviors, drugs showing partial agonism, such as VRX, are expected to balance serotonergic action upon these receptors in order to facilitate anxiolytic and antidepressant effects.

Similar to 5-HT1B receptors, 5-HT1D serotonin receptors are localized on presynaptic terminals of dorsal raphe nucleus fibers, although they are slightly less abundant [52]. Characteristically, 5-HT1D receptors are expressed on trigeminovascular nerve
endings and are targeted by antimigraine drugs (e.g. sumatriptan), in order to regulate the activity of cerebral vascular smooth muscle contraction to counteract vascular-generated cephalalgia [53]. Some studies, however, reported 5-HT₃D central localizations in the globus pallidus and substantia nigra pars reticulata, where they appear to be located on GABAergic striatal terminals, as well as in nonpyramidal neuron of the neocortex [54,55]. According to these data, 5-HT₁D agonists have been described to inhibit GABA cortical release, which may be prevented by antagonists, both actions possibly having physiological relevance in anxiety disorders [56]. A specific increase of 5-HT₁D receptors expression (together with 5-HT₁A, 5-HT₁B, 5-HT₂A, and 5-HT₄ receptors) has been described in animal models of heightened stress resilience [57]. According to some contrasting studies in which 5-HT₁D agonists could/could not exacerbate obsessive-compulsive symptoms in patients [58,59], an implication in the pathophysiology of obsessive-compulsive disorder has been suggested for these receptors [60]. Moreover, sumatriptan administration has been reported to aggravate anxiety symptoms in patients suffering from panic disorder [61]. Therefore, antagonism at 5-HT₁D receptors, as displayed by VRX, may have attenuating effects on anxiety symptoms.

Differently from all the other 5-HT receptors, which are seven-transmembrane passages-metabotropic receptors, 5-HT₃ receptors may be considered members of the cys-loop family of ligand-activated ion channels, which also includes nicotinic acetylcholine receptors and GABA-A receptors [62]. The 5-HT₃ receptor ion channel is composed of five subunits among six identified cDNA encoded units (A, B, C, D, E, and F) [63], which have been characterized as possessing multiple splicing variants originating several channel combinations. To date, homomeric 5-HT₃A subunit-formed receptors have been described [64], as well as heteromeric complex formed by all the other subunits together with the 5-HT₃A subunit [65–67]. However, current functional studies principally refer to two isoforms of 5-HT₃ receptors, the 5-HT₃A and 5-HT₃AR receptors, which represent the most diffused ones, both characterized as cation-permeable (Na⁺, K⁺, and Ca₂⁺) channels with different conductances and Ca₂⁺ permeabilities [68,69]. Early studies described a broad distribution of 5-HT₃ receptors in the brain, with high densities in the brainstem areas (nucleus tractus solitarius, area postrema, and spinal trigeminal nucleus) that are mainly involved in emesis and migraine [70,71], as well as in the vagal afferents of the peripheral nervous system that control the Bezold–Jarisch reflex [72]. More recent reports demonstrated specific distribution of 5-HT₃ receptors in limbic regions (hippocampus, amygdala, nucleus accumbens, and caudate-putamen), where they might have peculiar role in neuron–neuron synchronic integration through gamma oscillations [73], in glutamate-dependent synaptic plasticity [74], and in the formation of emotional memories [75]. Furthermore, 5-HT₃ receptors have peculiar presynaptic subcellular localization in the most part of brain regions, thereby controlling neurotransmitters release, except for the hippocampus, where they have been mainly detected postsynaptically in dendrites [76]. Last but not least, the broad distribution of 5-HT₃ receptor in the gastroenteric tract accounts for the essential role of these receptors in controlling gastrointestinal peristalsis and motility, as well as in the pathophysiology of functional and somatoform anxiety-linked gastroenteric disorders, such as the irritable bowel syndrome [77]. Extensive evidence points out the crucial involvement of 5-HT₃ receptors in the pathophysiology of anxiety behaviors, alone or included in broad syndromes, such as depression or gut comorbidities [78]. Indeed, animal studies described powerful effects of 5-HT₃ blockade in the inhibition of limbic hyperactivity responses generating anxiety behaviors [79], and 5-HT₃ knock-out animals have been demonstrated to display anxiety phenotypes [80]. Based on these data, several drugs with antagonist activity at 5-HT₃ receptors have been demonstrated to be effective in treating anxiety disorders [81,82].

5-HT₇ receptors have been the last CAMP-activating, seven-transmembrane passages, G-protein-coupled serotonin receptors to be discovered by targeted DNA analysis [83]. Four splice variants of 5-HT₇ receptor (namely 5-HT₇A, 5-HT₇B, 5-HT₇C, and 5-HT₇D) have been detected in humans, with different lengths of C-terminals [84], and different polymorphic variants, among which some having pharmacological interest because of altered binding to agonists [85]. 5-HT₇ receptors have high expression in the central nervous system, particularly in the hypothalamus (suprachiasmatic nucleus), thalamus, hippocampus, and cerebral cortex [86–88], as well as in the ileum, spleen, blood vessels and lymphocytes, and endocrine glands [89]. Also, some distribution of 5-HT₇ receptors has been detected in the raphe nucleus [90], with probable function of controlling serotonin release. In the hippocampus, 5-HT₇ receptors appear to be specifically located in cell bodies of CA1 pyramidal neurons [91]. By means of distribution- and ligand-based studies, it has been possible to implicate 5-HT₇ receptors in specific brain functions, such as circadian rhythms regulation, thermoregulation, endocrine regulation due to hypothalamic localizations, as well as sleep and mood regulation due to thalamic localization [92], and memory and learning due to hippocampal detection [93]. Animal 5-HT₇ knockout models have been demonstrated to display anxiety-like behaviors [94], as well as 5-HT₇ antagonists have been described to induce anxiolysis in animal behavioral tests [95] and to modulate the formation of emotional learning [96]. Thus, 5-HT₇ antagonists could be considered valuable compounds for the treatment of anxiety disorders.

Finally, its activity as NET may play a role in enhancing depressive symptoms both in patients with anxiety in comorbid MDD and in those patients affected with ADHD, frequently comorbid with anxiety disorders [25]. In addition, NET inhibition may reduce noradrenergic hyperactivity often responsible for the onset of numerous central symptoms of anxiety, such as nightmares, hyperarousal states, flashbacks, and panic attacks [25]. This activity may be explained due in part to its activity in desensitizing postsynaptic β and α₁, noradrenergic receptors [18,19].

Additional pharmacodynamic profiling of VRX revealed a modest binding affinity to noradrenergic β₂ receptors but a potent binding affinity at noradrenergic β₁ receptors (Ki = 46 nmol/l). However, the affinity for β₁ receptor could not be at present translated to an obvious pharmacology in vivo [97].

Pharmacokinetics and metabolism

VRX has a favorable pharmacokinetic profile with dose-proportional and linear exposure, moderate oral bioavailability
(around 75%), being 98% protein bound. There was no clinically meaningful effect of food on the pharmacokinetics of VRX, suggesting that it can be administered with or without food [98,99]. After oral intake, VRX is absorbed in the gastrointestinal tract, by showing an extended absorption phase and a peak plasma concentration in about 3–16 h ($T_{\text{max}}$) [98]. The exposure ($C_{\text{max}}$ and area under curve) increased linearly with dose (2.5–60 mg). The steady-state concentration is achieved in about 2 weeks. It exerts a medium clearance, a large volume of distribution (approximately 2600 l), and a long elimination half-life of around 57–66 h [100]. VRX undergoes extensive metabolism, primarily through oxidation and subsequent glucuronidation. It is mainly metabolized in the liver by at least five cytochrome P450 enzymes: e.g. CYP2D6 (IC50 = 34 μM), CYP1A2 (IC50 > 40 μM), CYP2C9 (IC50 = 15 μM), CYP3A4 (IC50 > 40 μM), and CYP2C19 (IC50 > 40 μM) [100–102]. VRX is metabolized, mainly through the CYP2D6 pathway, to its major carboxylic acid metabolite, LuAA34443 (3-methyl-4-(2-piperazine-1-yl-phenylsulfanyl)-benzoic acid), which is considered to be much less pharmacologically active and incapable of crossing the blood–brain barrier. LuAA34443 shows a similar half-life as VRX but a lower accumulation at steady state. A minor metabolite, LuAA39835, showed similar 5-HT transporter inhibition to the parent compound, although it is not expected to penetrate the blood–brain barrier. One-third of the drug is excreted in the feces (around 26%) while two-thirds in the urine (approximately 59%), mainly as glucuronides [103]. VRX demonstrated a low drug–drug interaction potential. In fact, it has no significant effect on the pharmacokinetics of ethinyl estradiol/levonorgestrel, bupropion, or omeprazole. In addition, coadministration of VRX did not alter the pharmacokinetics of warfarin or aspirin [104].

**Dosage and administration**

VRX is marketed in pink, yellow, orange, and, red oval, film-coated tablets, based on the strength, as it is available as 5, 10, 15 (not available in USA), and 20 mg immediate release tablets. The recommended initial dose is usually 10 mg administered orally once daily without regards to meals. The dosage can be increased gradually to a maximum of 20 mg daily if tolerated. The dosage should be decreased by 50% for CYP4502D6 poor metabolizers. Discontinuation of higher doses should be gradual, but abrupt discontinuation of 10 mg daily has been recommended.

The present systematic review aims here to provide an updated review on clinical studies on VRX in the treatment of GAD.

**Methodology**

**Search sources and strategies**

A systematic review was here conducted according to the methods recommended by the Cochrane Collaboration [105] and documented the process and results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [106]. Literature searches were performed by using the following electronic databases (last update: December 2015): MEDLINE, SCOPUS, ScienceDirect, and PubMed. We combined the search strategy of free text terms and exploded MESH headings for the topics of Vortioxetine, Generalized Anxiety Disorder, and Anxiety as follows: (((Vortioxetine[Title/Abstract] OR Lu AA21004[Title/Abstract]) AND antidepressant [Title/Abstract]) OR brindellix[Title/Abstract]) AND (antidepressant [Title/Abstract] OR anxiety [Title/Abstract]). The strategy was first developed in MEDLINE and then adapted for use in the other databases. No restrictions by year of publication or language were applied to any search. Studies published through 20 December 2015 were included. Further studies were retrieved from reference listing of relevant articles and consultation with experts in the field and/or manual search. In addition, in order to include unpublished studies, within the time frame of the electronic searches, additional hand searches were performed on websites of pharmaceutical companies, clinical trials repositories and registers, and regulatory agencies (e.g. www.clinicaltrials.gov, US FDA website), as well as on GoogleScholar.

**Study selection**

We considered studies that included VRX treatment for GAD. We examined all titles and abstracts and obtained full texts of potentially relevant papers. Working independently and in duplicate, two reviewers (L.O. and C.T.) read the papers and determined whether they met inclusion criteria. Duplicate publications were properly excluded. All English-language articles identified by the data sources, reporting original data related to VRX, were evaluated in the present review. All experimental and observational study designs were included apart from case reports. Randomized, controlled clinical trials involving humans were prioritized in the present systematic review. Narrative and systematic reviews, letters to the editor, and book chapters were excluded.

**Data extraction and management**

L.O. and C.T. independently extracted the data on participant characteristics, intervention details, and outcome measures. Disagreements were resolved by discussion and consensus with a third member of the team (D.D.). Data were collected using an ad hoc-developed data extraction spreadsheet.

**Characteristics of included studies**

From 442 potentially relevant records from the search of databases and additional sources, 171 were excluded on the basis of title or abstract, and 262 were excluded because duplicates. The remaining nine studies were retrieved for more detailed evaluation. Overall, five studies, of which four were short-term randomized clinical trials (RCTs) and one long-term relapse prevention study, met the inclusion criteria. Furthermore, of the 54 records obtained from ClinicalTrials.gov, among the seven trials retrieved here, five were duplicates of those identified by the aforementioned search. The main characteristics of the seven studies retrieved here are reported in Table 1.
<table>
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<tbody>
<tr>
<td>Clinical trials.gov ID number</td>
<td>Double-blind, placebo-controlled, fixed-dose study – phase III</td>
<td>Double-blind, placebo-controlled, fixed-dose study – phase III</td>
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<tr>
<td>NCT00744627</td>
<td>N0744627</td>
<td>N0731120</td>
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<tr>
<td>Study design</td>
<td>Study evaluating efficacy and safety of a single dose of VRX in acute treatment of adults with GAD</td>
<td>Study evaluating efficacy and safety of VRX in the treatment of GAD</td>
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<tr>
<td>End point classification</td>
<td>Efficacy/safety study</td>
<td>Safety/efficacy study</td>
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<tr>
<td>Aim/hypothesis</td>
<td>Study evaluating efficacy and safety of a single dose of VRX in acute treatment of adults with GAD</td>
<td>Study evaluating efficacy and safety of VRX in the treatment of GAD</td>
</tr>
<tr>
<td>Sample characteristics</td>
<td>N: 301 Age: ≥18 years Diagnosis: GAD</td>
<td>N: 457 Age: ≥18 years Diagnosis: GAD</td>
</tr>
<tr>
<td>Study description</td>
<td>Length: 8 weeks Experimental: fixed dose (5 mg/day) of oral VRX (n = 150) Comparator(s): PBO (n = 151)</td>
<td>Length: 8 weeks Experimental: 2.5 mg/day (n = 152); 10 mg/day (n = 152) Comparator(s): PBO (n = 153)</td>
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<tr>
<td>Primary</td>
<td>HAM-A</td>
<td>HAM-A</td>
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<tr>
<td>Secondary</td>
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<td>Percentage of responders in HAM-A total score at week 8</td>
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<tr>
<td>Findings</td>
<td>No statistically significant improvement neither to the primary nor to secondary end points</td>
<td>No statistically significant improvement neither to the primary nor to secondary end points</td>
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A statistically significant improvement from baseline to week 8 in primary and secondary efficacy end points in VRX vs. PBO (p < 0.001)

(Continued)
<table>
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<tr>
<th>Clinical trials.gov ID number</th>
<th>Study design</th>
<th>End point classification</th>
<th>Aim/hypothesis</th>
<th>Sample characteristics</th>
<th>Study description</th>
<th>Primary Findings</th>
<th>Secondary Findings</th>
</tr>
</thead>
</table>
| NCT00788034 (completed)     | Double-blind, placebo-controlled, parallel-group, study – phase III | Safety/efficacy study | Study evaluating efficacy of VRX in preventing relapse in patients with GAD who had responded to acute VRX treatment | N: 459  
Age: ≥18 years  
Diagnosis: GAD | Length: 24 weeks  
Experimental: 5 or 10 mg/day (n = 229)  
Comparator(s): PBO (n = 230) | Percentage of relapse after 24-week treatment | A statistically significant effect of VRX vs. PBO in the prevention of relapse |
| NCT00730691 (completed)     | Double-blind, placebo-controlled, parallel-group, active-referenced, fixed-dose study – phase III | Safety/efficacy study | Study evaluating efficacy and safety of three doses of VRX in the acute treatment of adults with GAD | N: 781  
Age: 18–65 years  
Diagnosis: GAD | Length: 8 weeks  
PBO-matching Fw-up: 1 week  
Experimental: 2.5 mg/day (n = 156); 5 mg/day (n = 156); 10 mg/day (n = 156) of oral VRX  
Comparator(s): PBO (n = 157); DLX 60 mg/day (n = 156) | HAM-A | No statistically significant improvement neither to the primary nor to secondary end points |
Age: ≥18 years  
Diagnosis: PD | Length: 10 weeks  
Experimental: 5–20 mg/day  
Comparator(s): none | PDSS | QLOS  |
| NCT01491035 (completed)     | Open label, phase II | Safety/efficacy study | Study evaluating pharmacokinetics and tolerability of VRX in child and adolescent patients with MDD or anxiety disorder | N: 48  
Age: 7–17 years  
Diagnosis: depressive or anxiety disorder | Length: 8 weeks  
Experimental: 5 mg/day vs. 10 mg/day vs. 15 mg/day vs. 20 mg/day  
Comparator(s): none | C_{max}  
AUC  
T 1/2  
Oral clearance | N/A  |

1If available.

VRX: vortioxetine; n: sample number; N/A: not available; GAD: generalized anxiety disorder; Fw-up: follow-up; PBO: placebo; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; CGI-I: Clinical Global Impression of Illness Scale; SDS: Sheehan Disability Scale; SF-36: 36-Item Short-Form Health Survey; CGI-S: Clinical Global Impression of Severity Scale; AEs: adverse events; VS: vital signs; PDSS: Panic Disorder Severity Scale; QLOS: Quality of Life Scale; MOSES: Multidimensional Observation Scale for Elderly Subjects; AUC: area under the curve; C_{max}: maximum serum concentration; T 1/2: half-life.
Preclinical studies

As mentioned previously, most of the pharmacodynamics properties displayed by VRX suggest possible anxiolytic effects. Indeed, although the most part of preclinical studies focused on antidepressant features of VRX, some demonstrated peculiar anxiolytic potential of the compound. In a recent study by Guillox et al. [112], VRX has been demonstrated to counteract both spontaneous and novelty-related anxiogenic stimuli, respectively, in the open-field and the novelty-suppressed feeding behavioral tests, when acutely administered. Notably, these effects were displayed at doses corresponding to 60–70% of SERT occupancy, thereby suggesting a mechanism not relying on it, and disappeared at high dosages, thus paralleling the biphasic effects of 5-HT receptors antagonists in as well as the dose-dependent effects of 5-HT receptors antagonist in preclinical anxiety paradigms [95]. Moreover, in the same study, the anxiolytic effects displayed by VRX persisted in chronic paradigm, with the same peculiar dose- and time-dependent features.

The antagonist action at 5-HT receptors by VRX has also been demonstrated to play a crucial role in the modulation of circadian rhythms, whose dysfunction is considered essentially relevant in the pathophysiology of anxiety disorders. Indeed, the acute administration of VRX has been reported to induce a phase shift in circadian rhythms in animal models (i.e. a delayed timing), which could be abolished by 5-HT agonists [113]. Moreover, the circadian delay induced by VRX might be mimicked by the simultaneous administration of 5-HT partial agonists plus 5-HT antagonists, but not by each compounds administered alone, thus suggesting that the effects of VRX on circadian rhythms may derive by a complex interplay among multiple 5-HT receptors modulation exerted by this compound.

The multimodal regulation of serotonin receptors by VRX has also been correlated to the improvement in memory formation, whose impairment in fear-elaborating neurocircuits is considered at the basis of anxiety pathophysiology [114]. Indeed, the administration of VRX to rats 1 hour before the administration of a contextual fear conditioning test has been demonstrated to improve memory acquisition in the retention test [115]. Moreover, successive studies have also demonstrated that VRX, but not escitalopram or duloxetine, may restore memory impairment caused by serotonin depletion [116], and these effects are dose dependent and most likely rely on VRX modulation of 5-HT1a and 5-HT3 receptors [117].

To further corroborate the peculiar characteristics of VRX as anxiolytic drug, a recent study has also demonstrated that only this compound, as well as amitriptyline, may attenuate anxiety behaviors in animal models of progesterone withdrawal (which is a classical model of hormone-related dysphoric behaviors characterized by anxiety, irritability, anhedonia, and depression), whereas duloxetine and fluoxetine have been reported as ineffective [118]. Again, these effects might be attributed to the peculiar 5-HT3 receptors antagonist and 5-HT1a partial agonist action.

Therefore, although more specific studies are needed, preclinical studies demonstrate a peculiar anxiolytic action of VRX, which could be possibly due to the specific multimodal interaction with serotonin receptors exerted by this compound.

Clinical efficacy

Phase II studies

A phase II, open-label study (NCT01491035) whose results are still ongoing evaluated the pharmacokinetics of VRX and its metabolites in connection with multiple oral dosing in child and adolescent patients with a diagnosis of depressive or anxiety disorders. There are not still available results on outcomes.

Phase III studies

RCT – placebo controlled

A multinational, randomized, parallel-group, placebo-controlled, fixed-dose (5 mg/day), 8-week study [107] (NCT00744627) was conducted on 301 patients with a primary diagnosis of GAD and an Anxiety Rating Scale (HAM-A) total score ≥20 at baseline. Subjects were randomized to placebo (n = 151) or 5 mg/day of VRX (n = 150). A statistically significant difference between VRX and placebo was reported from baseline to week 8 in HAM-A total score (p < 0.001) and Clinical Global Improvement of Improvement (CGI-I) score (p < 0.001). In addition, subjects who received VRX had statistically significant improvement (vs. placebo) from baseline to week 8 in all key secondary efficacy end points (change from baseline at week 8 in HAD anxiety subscore, CGI-I, Sheehan Disability Scale [SDS] total score, HAM-A response rate, HAM-A total score, SF-36 social functioning subscore; p < 0.05). HAM-A response rates at week 8 in the VRX group was higher than in the placebo group (odds ratio [OR] = 2.393; p < 0.001). The response rate was 61.7% in VRX group (vs. 39.9% in placebo group). Subjects treated with VRX were more likely to achieve remission by week 8 (OR = 1.958). The remission rate was 30% in VRX group (vs. 18% in placebo group).

A randomized, double-blind, fixed-dose study (NCT00731120) [108] comparing the efficacy and tolerability of VRX 2.5 and 10 mg in acute treatment of GAD assessed 457 subjects, randomly assigned to 2.5 mg/day vs. 10 mg/day vs. placebo. No statistically significant improvement was achieved concerning VRX over placebo on the primary and secondary end points (respectively, p = 0.279 for 2.5 mg/day and 0.306 for 10 mg/day).

A multicenter, placebo-controlled, parallel-group, double-blind trial evaluated the safety and efficacy of a fixed dose of 5 mg VRX on 304 subjects with a primary diagnosis of GAD [109] (NCT00734071). No statistically significant differences in HAM-A total score changes from baseline to week 8 were observed in the VRX group vs. placebo (p = 0.518). In addition, no statistically significant differences were observed for any secondary end point. HAM-A response rates at week 8 were 50% in the placebo group (vs. 53% in VRX group; p = 0.602). HAM-A remission rates at week 8 were 22 vs. 26%, respectively (p = 0.517). The authors did not describe any clinical advantage for the 5-mg dose of VRX for the treatment of subjects with GAD compared to placebo.

A long-term (24–56 weeks), double-blind, randomized, fixed-dose, placebo-controlled relapse prevention study [110] (NCT00788034) evaluating the efficacy of VRX in the prevention of relapse in patients with GAD who had previously...
responded to an initial 20-week, open-label, 8-week, flexible-dose (5–10 mg/day) treatment period with VRX (HAM-A total score ≤10 at both weeks 16 and 20). The study initially recruited 687 outpatients from 80 centers in 10 countries and included in the first acute treatment (20 weeks, open label). Subsequently, 459 patients who responded were randomized to placebo (n = 230) or fixed dose (5 or 10 mg/day) of VRX (n = 229) in the second phase of study (relapse prevention, 24–56 weeks, double blind). All patients were then monitored and assessed during a 4-week safety follow-up. During the open-label period, the mean HAM-A total score and Clinical Global Impression of Severity (CGI-S) decreased at week 20. At week 20, 79.9% of patients had responded (HAM-A ≥ 50% decrease from baseline), and 60.5% had achieved remission (HAM-A total score ≤7). A statistically significant effect of VRX compared to placebo was reported on the time to relapse in the double-blind period (p < 0.0001). The risk of relapse in the placebo group was almost three times that for patients in the VRX group (p < 0.0001). The proportion of patients who relapsed was significantly lower in the VRX group compared to placebo group (15 vs. 24%; p < 0.0001). A statistically significant effect of VRX was reported in stable responders on the time to relapse in VRX-treated patients vs. placebo-treated (p < 0.001). Stable responders who relapsed was lower in VRX group vs. placebo one (13 vs. 33%).

**RCT – placebo controlled, active reference**

A multicenter, randomized, double-blind, placebo-controlled, duloxetine-referenced, phase III study [111] (NCT00730691) was carried out on 781 patients randomized to placebo group (n = 157), 2.5 mg/day VRX (n = 156), 5 mg/day VRX (n = 156), 10 mg/day VRX (n = 156), and 60 mg/day duloxetine group (n = 156). No statistically significant changes from baseline in HAM-A total score were reported in the three VRX treatment groups. Similar results were reported among the three VRX groups regarding to all key secondary efficacy end points. According to this study, the effects of VRX on most efficacy outcome measures were not statistically significantly different from that of placebo at daily doses of 2.5, 5, and 10 mg in patients with GAD. However, duloxetine 60 mg significantly improved the primary end point (p < 0.05) vs. placebo.

**Phase IV studies**

A 10-week, open-label, flexible dose (5–20 mg/day) adaptive study is still evaluating the efficacy of VRX in subjects with PD (NCT02395510).

**Safety and tolerability**

Clinical studies suggest that VRX has a good safety and tolerability profile. During the open-label period of study by Baldwin et al. [110], 8.7% of patients withdrew because of adverse events (AEs), mainly mild to moderate. These particularly included nausea (27.1%) and headache (17.6%). Other AEs reported included diarrhea (7.4%), dizziness (6.1%), insomnia (3.5%), and sexual dysfunction (2.6%), i.e. decreased libido, erectile dysfunction, delayed ejaculation, loss of libido, anorgasmia, and decreased orgasmic sensation. Serious AEs were described in 1.5% of patients (n = 10), consisting of one committed suicide, suicidal idea-}

[94x506]tion (n = 4). Whilst during the double-blind period of the same study, the incidence of AEs was similar in VRX-treated and placebo-treated patients (53.9 vs. 55.5%, respectively). Most AEs were mild to moderate. The most reported AEs statistically significantly higher in VRX group vs. placebo group were influenza (12 vs. 6%, respectively; p < 0.05) and accidental overdose (5.2 vs. 1.3%; p < 0.05). Three of four patients reported serious AEs in the VRX group vs. placebo. During both the open-label period and the double-blind period, no clinically significant mean changes in clinical safety laboratory values, vital signs, weight, or ECG values were described [109]. According to another phase III study [118], the most frequently reported treatment-emergent AEs were, respectively, in VRX and placebo group: nausea (11.3 vs. 3.3%), headache (6.7 vs. 6%), and dizziness (5.3 vs. 2.7%). The most common AEs in the VRX group vs. placebo included nausea, headache, dry mouth, diarrhea, dizziness, nasopharyngitis, somnolence, constipation, dyspepsia, upper respiratory tract infection, vomiting, and fatigue [111]. The most frequently reported AEs included nausea (25% in VRX-group vs. 4.6% in placebo-group), headache (10.1 vs. 8.6%), dizziness (8.1 vs. 3.3%), and dry mouth (8.1 vs. 3.3%) [109]. A further study [108] described nausea (24.3% at 10 mg/day, 15.9% at 2.5 mg/day, and 8.5% with placebo), dry mouth (7.9% at 10 mg/day, 9.3% at 2.5 mg/day, and 11.1% with placebo), headache (11.8% at 10 mg/day, 13.2% at 2.5 mg/day, and 11.1% with placebo), diarrhea (11.2% at 10 mg/day, 8.6% at 2.5 mg/day, and 7.2% with placebo), constipation (5.9% at 10 mg/day, 2.6% at 2.5 mg/day, and 3.9% with placebo), and vomiting (5.3% at 10 mg/day, 2.0% at 2.5 mg/day, and 2.6% with placebo), as the most common reported AEs.

A pooled study evaluating the incidence of treatment-emergent sexual dysfunction (TESD) during short-term (8 weeks) treatment with VRX compared to placebo, in seven trials carried out on subjects affected with MDD or GAD [119]. Overall, the incidence of TESD in VRX-treated groups combined (37.1%) was not significantly different from placebo. The risk of the onset of TESD in the 5-mg VRX group was lower than in the placebo group and non-inferior to placebo. The effects of VRX treatment in patients with pre-existing sexual dysfunction at baseline were similar to placebo. Overall, across the analyzed and pooled trials, VRX 5–20 mg was associated with an approximately 5% increase in incidence of TESD over placebo in patients without sexual dysfunction at baseline. However, the incidence of TESD relative to placebo generally increased with increasing VRX dose in patients without sexual dysfunction at baseline.

Overall, in clinical trials focusing on GAD patients, VRX is generally well tolerated at 5 mg/day [107,109]. Furthermore, according to Theunissen et al. [120], VRX does not appear to affect driving, cognitive, and psychomotor performance in 24 healthy subjects over a 15-day period.
Conclusion

At writing time, a paucity of studies about VRX in the treatment of GAD has been published so far. The generalizability of results to the broad population of patients with anxiety symptomatology and GAD is limited because of few RCTs available so far as well as sample characteristics, as patients aged <18 years or >65 years were not included, or patients at risk of suicidal behavior, or those with comorbid MDD. In addition, available findings are still contrasting in terms of the potential efficacy in anxiety disorders and GAD [107–111]. Only two clinical studies reported a significant improvement in anxiety symptomatology [107,110].

Furthermore, findings coming from preclinical studies are still limited, most of them mainly exploring the antidepressant effects of VRX, with only few ones specifically investigating its anxiolytic efficacy [95,112–118]. In particular, data regarding to the antianxiety properties of VRX are often extrapolated from parts of preclinical antidepressant-specific paradigms. At the best of our knowledge, although several behavioral models of anxiety have been developed, the current ‘models’ may be affected by the concept that anxiety is peculiarly a subjective status. Overall, these models may be based on unconditioned (not needing training and owning a high ethological validity; i.e. open field and elevated plus mazes; social interaction, predator avoidance, freezing test; etc.) or conditioned responses (influenced by cognitive processes and needing training; i.e. startle response, defensive burying, passive/active avoidance tests; etc.). Furthermore, recent advances in genetic technologies favored the development of specific animal strains that display ‘anxiety’ behaviors that could be used to be tested with putative anxiolytics drugs (i.e. HAB or high anxiety behavior rats; Syracuse rats; etc.). Therefore, based on the above-mentioned anxiety models, more specific paradigms could be applied to better evaluate the anxiolytic effects of VRX.

The pharmacological profile of VRX is notably different from that of other known antidepressants. VRX was specifically designed to combine a low occupancy of the 5-HT transporter, 5-HT3 receptor antagonism, and 5-HT1A partial receptor agonism. Given its multimodal and peculiar pharmacological profile, VRX has been already approved for MDD in adults [120]. Furthermore, some clinical trials carried out on MDD patients showed a significant improvement in comorbid anxiety symptoms [121–124] by suggesting a promising research field also for the treatment of anxiety disorders. Despite the fact that GAD and MDD may share some common biological underpinnings and VRX owns a promising mechanism of action as alternative option for patients with GAD, findings available so far are still contrasting [107–111]. Therefore, further RCTs are needed in order to better evaluate its efficacy in GAD. In particular, active-reference RCTs comparing current clinically effective anxiolytics vs. VRX should be considered. In addition, RCTs and open-label trials specifically evaluate short- and long-term VRX efficacy among GAD patients and compare clinical samples with and/or without comorbid MDD, in order to better discriminate the underlying substrates of the clinical improvement of anxiety symptomatology.

Overall, tolerability of VRX both in short- and in long-term studies carried out on patients affected with GAD was similar [107–111]. The tolerability of VRX was not different from that of placebo in the long-term treatment of patients with GAD, despite the longer exposure of patients randomized to VRX [110].

VRX is well tolerated and appears to have relatively little potential for adverse drug interactions. Though there is no suggestion of superiority over active comparators, most studies suggest that there is a clinically meaningful advantage in terms of tolerability [111]. The most common AEs reported (with an incidence ≥5% and at least twice the rate of placebo) comprised nausea (approximately ranging 11–27%, even at the lowest dose), headache (ranging 6.7–17.6%, dry mouth (8–9%), dizziness (5.3–8.1%), diarrhea (7–8%), constipation (2.6–6%), vomiting (2–6%), and sexual dysfunction (22–34% among women vs. 16–29% among men). Rare but serious side effects include serotonin syndrome (muscle tightness, fever, seizures, and death), increased risk of bleeding due to impaired platelet aggregation, increased risk of syndrome of inappropriate antidiuretic hormone secretion, hyponatremia (headache, weakness, difficulty concentrating, and remembering), induced manic episode in bipolar patients, and central nervous system depression [107–111]. It should be suggested for patients who cannot tolerate psychomotor/cognitive impairment or cardiac side effects, and it may be helpful for older patients [125,126]. However, further studies specifically and directly comparing the efficacy and AEs of VRX with current clinically effective anxiolytics should be performed in order to better balance safety and tolerability VRX profile.

Expert commentary

It has been well established that GAD is a chronic and disabling disease that may be associated with psychological and physical symptoms. Furthermore, it has also been documented that response and remission rates in patients affected with GAD are often disappointing. Therefore, the ‘ideal drug’ should have a rapid onset of effects, with few/absence of drug interactions, be effective in achieving remission of symptomatology and in enhancing quality of life, and should not affect psychological/physical symptomatology, as well as determining disabling AEs. Moreover, it should be effective in preventing relapse, not determining discontinuation symptoms and/or dependence and/or tolerance [11].

Expectations from this new multimodal antidepressant go beyond its efficacy in the MDD patients, already hugely demonstrated [127,128]. Although data coming from preclinical trials appear promising [112,114–117], clinical trials do not appear to confirm these findings.

Five-year view

In the next 5 years, we can expect that VRX will continue to be tested and evaluated among patients affected with anxiety symptomatology with or without comorbid MDD. Future research directions should provide more RCTs specifically targeted to clinical sample with GAD, in order to assess the efficacy of this new antidepressant in a larger sample, as well as evaluate
Despite numerous pharmacological agents, response rates in the treatment of GAD, as well as discriminate how the treatment of anxiety dimension may be influenced by the mood dimension in comorbid MDD patients. Furthermore, open-label trials should be provided to assess its safety and tolerability profile in the subgroup of patients. In addition, longer-term studies are needed to demonstrate that the beneficial effects of VRX are maintained over time.

Finally, the peculiar multimodal pharmacological activity of VRX may promote the development of newer drugs owning an intrinsic multimodal activity, able to improve both depressive and anxiety symptomatology.

Key issues

- Despite numerous pharmacological agents, response rates to initial treatment with an SSRI or SNRI are still inadequate in the treatment of GAD
- VRX exerts reuptake inhibition on the serotonin transporter, increasing the level of serotonin in the neuronal synapse as well as selectively binding to a variety of other serotonin receptors (5-HT3, 5-HT1D, 5-HT7, 5-HT1B, 5-HT1A)
- The antianxiety effects of VRX have been consistently observed in many MDD trials.
- VRX acts as partial agonist at 5-HT1A receptors, which are involved in anxiety-like behaviors and in the susceptibility to anxiety disorders, displaying anxiolytic effects.
- Partial agonist activity at 5-HT1B receptors may exert effects in modulating stress sensitivity, mood, anxiety and aggression by inhibiting the release of serotonin, norepinephrine, GABA, acetylcholine and glutamate.
- VRX exerts antagonist activity at 5-HT1D which may attenuate effects on anxiety disorders.
- The antagonistic activity at 5-HT3 receptors, which have an essential role in controlling gastrointestinal peristalsis and motility, may attenuate functional and somatoform anxiety-linked gastrointestinal disorders.
- Preclinical studies showed promising antianxiety effects of VRX in the treatment of GAD animal models.
- VRX displays a favorable side effect pattern associated with a low risk of pharmacological interactions.
- However, RCT of GAD so far conducted showed inconsistent findings regarding the efficacy of VRX.
- Further clinical studies are needed in order to better establish VRX efficacy in GAD and other anxiety disorders.

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