Vortioxetine as a new frontier in the treatment of chronic neuropathic pain: a review and update

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Abstract: Chronic neuropathic pain (CNP) is a disabling medical condition that impairs the health-related quality-of-life of affected patients. A high prevalence of anxiety, depression, sleep disturbance and cognitive impairment has frequently been reported in association with CNP, making the management of this disease complex and often multidisciplinary. Dual-acting agents such as selective serotonin and noradrenalin reuptake inhibitors (SNRIs) are considered particularly useful in the modulation of pain and in treatment of the mood disorders frequently associated with CNP. Recent evidence suggests that the top-down inhibitory control of pain involves the engagement and enhancement of descending endogenous opioidergic, cannabinoid and serotonergic systems, with the effect of serotonin being particularly related to the receptor subtypes that are preferentially activated; indeed serotonin induces analgesia via activation of 5-HT7 receptors and hyperalgesia via activation of 5-HT3 receptors. Vortioxetine (VO) is a novel multimodal serotonergic antidepressant with a unique mechanism of action. It has been demonstrated recently in experimental and clinical studies to have efficacy on pain hypersensitivity and on mood disorders. This drug inhibits the serotonin transporter with a high affinity, antagonises the 5-HT3, 5-HT1D and 5HT7 serotonin receptors, and activates the 5-HT1A and 5-HT1B receptors. In clinical studies, VO has proved effective at a dose of 10–20 mg/daily in short- and long-term treatment of patients with chronic orofacial pain, demonstrating a higher rate of clinical response and remission, a better acceptability, safety rate and tolerability, and a lower latency of action compared with other antidepressants. In the light of these recent findings, VO may be considered as a new pharmacological treatment also in relation to various types of CNP, particularly in elderly patients with concomitant mood disorders and cognitive impairment. The purpose of this review is to provide an up-to-date overview of the pharmacology and clinical applications of VO and to highlight its potential therapeutic properties and advantages in the management of CNP.

Keywords: chronic neuropathic pain, vortioxetine, depression, anxiety, cognitive impairment

Introduction
Chronic pain is one of the most widespread disorders throughout the world, with almost 18% of the general population in developed countries affected. Despite its high estimated prevalence, chronic pain management is still not completely satisfactory, probably due to the variety of chronic pain conditions with different etiologies (neuropathic, visceral, musculoskeletal and cancer-related) and due to the pathophysiological mechanisms, which are only partially known. Neuropathic pain (NP) has been defined by the International Association for the Study of Pain (IASP) as ‘pain caused by a lesion or disease of the somatosensory nervous system’. Patients typically experience a distinct set of symptoms, such as burning and electrical-like sensations, and pain...
resulting from non-painful stimulations (such as light touching); the symptoms persist and have a tendency to become chronic and respond with increasingly less effectiveness to pain medications.

Despite the development of knowledge in relation to this topic, chronic neuropathic pain (CNP) continues to be a challenge for healthcare providers. Indeed, CNP is an extremely complex phenomenon, which is composed of both a perceptive and an emotional component and is therefore often associated with anxiety, depression and sleep disturbance. The coexistence of psychiatric comorbidities may aggravate the CNP symptomatology, which, if left untreated, contributes to worsen the quality-of-life of affected patients.

Therefore, in recent years, CNP management has been focused not only on the modulation of pain but also on the treatment of potentially associated mood disorders and sleep disturbance.

In this context, the use of antidepressants (ADs) has been considered a valid therapeutic option in the treatment of CNP and healthcare providers have begun to use these drugs outside their regulatory approval, adopting an off-label regimen.

Indeed, psychotropic drugs, particularly the selective serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), which act as central neuromodulators, have been demonstrated to be effective in relieving pain and in improving anxiety, depression and quality of sleep. However, the use of SSRIs and SNRIs and TCAs may be complex due to the difficulty in managing several potential side effects (for instance sleep disturbance, weight gain, QTc prolongation and sexual dysfunction), especially in elderly patients. The incidence of such side effects may, in turn, impair the patient’s adherence to the treatment and undermine the achievement of the treatment goals.

Vortioxetine (VO) is a novel multimodal serotonergic antidepressant, approved in the last decade in many countries worldwide for the treatment of major depression.

VO inhibits serotonin (5-HT) transporter (SERT), similarly to commonly used ADs, but, differently, it directly modulates the activity of 5-HT receptors. Due to its peculiar pharmacological profile, VO was recently classified among ‘the other antidepressants’ in the World Health Organisation (WHO) ATC/DDD Index 2018.

Recent experimental and clinical studies have shown that VO exerts antidepressant and pro-cognitive activities and that it is also effective in modulating pain hypersensitivity. Indeed, the efficacy of VO in the treatment of CNP is produced through the enhancement of the serotonergic transmission, the simultaneous inhibition of the 5-HT3 receptors and the modulation of the 5-HT7 receptors. In this context, VO may cause analgesia mediated by the 5-HT7 receptors and hyperalgesia mediated by the 5-HT3 receptors. Moreover, VO has exhibited a good tolerability profile, particularly in the elderly, since it does not affect cardiovascular, endocrine parameters and body weight.

In light of the recent evidence about this promising new psychotropic drug, the aim of this review is to provide an up-to-date overview on the pharmacology and clinical applications of VO and to highlight its potential therapeutic properties and advantages in relation to CNP management.

**Mechanism of action**

**Pharmacological and receptor binding profile**

VO shows new and unique multimodal pharmacological properties. Indeed, it acts as an inhibitor of SERT, sharing this mechanism with SSRI, SNRI and TCA, as well as direct modulator of the activity of multiple 5-HT receptor subtypes.

VO works as a modulator and stimulator of 5-HT, it also exerts its activity on the neurotransmission of the noradrenergic, dopaminergic, cholinergic, histaminergic, glutamatergic and gamma-aminobutyric acid (GABA)ergic systems in the relevant brain areas.

The binding affinities and functional activities of VO in rats are generally similar to those in humans; however, its affinities for the 5-HT7 and 5-HT1A receptors in rats are 10- to 15-fold weaker at comparable doses, suggesting that the action of VO towards these receptors could be stronger in human subjects.

In humans, VO inhibits SERT with a high affinity ($K_i = 1.6 \text{nM}$), increasing the levels of 5-HT in the post-synaptic space, similarly to other antidepressants. However, it is the only drug that can modulate 5-HT receptor activity directly, being a full agonist of 5-HT1A ($K_i = 15 \text{nM}$), a partial agonist of 5-HT1B ($K_i = 33 \text{nM}$), and an antagonist of the
5-HT3 ($K_i = 3.7 \text{nM}$), 5-HT7 ($K_i = 19 \text{nM}$) and 5-HT1D receptors ($K_i = 54 \text{nM}$). However, in rodents the binding affinity of VO is as follows: SERT ($K_i = 8.6 \text{nM}$); 5-HT1A ($K_i = 230 \text{nM}$); 5-HT1B ($K_i = 16 \text{nM}$); 5-HT3 ($K_i = 1.1 \text{nM}$); 5-HT7 ($K_i = 200 \text{nM}$); 5-HT1D ($K_i = 3.7 \text{nM}$). Previous experimental studies have highlighted that the antagonism towards the three 5-HT receptors leads to an increase in 5-HT levels and, as a consequence, enhances the serotonergic neurotransmission in the different forebrain regions.

Besides, the affinity of VO for the β1 adrenergic receptor is relevant only in the context of its side effects. When tested against a panel of 70 other G-protein-coupled receptors (GPCRs), transporters, enzymes, ion channels and kinases, VO displayed no pharmacologically relevant activity.

VO's binding affinity is dose proportional. Experimental clinical studies have shown that VO engages, preferentially, SERT and 5-HT3 at a lower dosage, between 5 and 10 mg, and engages all targets at a higher dosage of 20 mg. In positron emission tomography (PET) studies in healthy volunteers, VO at doses of 5, 10 and 20 mg/day demonstrated dose-dependent SERT occupancy rates in the brain, namely 50%, 53–65% and 80%, respectively, for each dose with EC$_{50}$ values ranging from 4.2 to 6.5 ng/mL.

The rank order potency of VO is as follows: 5-HT3 > SERT > 5-HT1B > 5-HT1A = 5-HT7.

VO in the treatment of mood disorders, cognitive impairment and sleep disturbance

Table 1 shows the multimodal mechanism of action of VO.

Experimental and clinical studies suggest that VO might exhibit simultaneously antidepressant, anxiolytic and pro-cognitive activities. Indeed, the blocking of SERT causes a wide release of 5-HT that stimulates the presynaptic somatodendritic inhibitory 5-HT1A receptors of the raphe nuclei, creating a negative feedback loop that reduces, at the beginning, the antidepressant effect of the SSRIs and SNRIs. Differently, VO beyond its action on SERT, works as an agonist of these receptors and accelerates the desensitisation and disinhibition caused by the 5-HT release, contributing to a reduction in the latency of action of this drug compared with other ADs.

In addition, the antagonism of the 5-HT7 further enhances serotonergic transmission with a synergistic antidepressant effects.

Moreover, VO is an antidepressant with a pro-cognitive effect, independently from any improvement in mood.

In animal models, acute, sub-chronic and chronic administration of VO exerts positive effects across a range of cognitive tasks. VO achieved enhancements in acquisition and retention of contextual fear memory, object recognition memory and visuospatial memory in rats and mice.

In humans, VO has demonstrated cognitive enhancing properties in seven short-term randomised controlled trials (RCTs) (6–12 weeks), three meta-analyses, and one open-label trial, with significant improvements in processing speed, executive control, verbal learning and recall domain in young and elderly patients with moderate to severe depression. These improvements, independent from the alleviation of depressive symptoms, represent a direct effect of VO and have been reported at doses across the clinically relevant dose range (5–20 mg/day) without a dose–response effect, suggesting that VO exerts its pro-cognitive and antidepressant actions via separate mechanisms.

The pro-cognitive activity of VO is related mainly to the blocking of the 5-HT3 receptors located in a subset of the GABAergic inhibitory interneurons, with a subsequent reduction in the GABAergic transmission, which can in turn disinhibit pyramidal neuronal activity and increase glutamatergic neurotransmission, long-term potentiation (LTP) and neuroplasticity in the prefrontal cortex and in the hippocampus. Moreover, the partial agonism toward the 5-HT1B receptors increases the release of 5-HT, glutamate, acetylcholine and histamine, indirectly of dopamine and noradrenaline, particularly in the prefrontal cortex and hippocampus, while the antagonism of 5-HT7 increases the acetylcholine and noradrenaline levels in the medial prefrontal cortex. The stimulation of cholinergic and histaminergic neurotransmission may further contribute to the pro-cognitive effect of VO.

The enhancing effect on noradrenergic neurotransmission is related not only to a partial agonism of 5-HT1B but also to the stimulation of the 5-HT1A and the blocking of the 5-HT3
Similarly, the indirect selective increase in the levels of dopamine in the frontal cortex and hippocampus is related not only to the effect on the 5-HT1B receptors but also to the agonism of the 5-HT1A receptors, which are known to increase extracellular dopamine upon stimulation. It has been demonstrated that VO considerably increases only the extracellular 5-HT levels in the nucleus accumbens in all the doses tested, without significantly affecting the noradrenaline and dopamine levels. Furthermore, recent studies have suggested that VO, like monoaminergic ADs, is able to promote the synaptic neuroplasticity of the brain. Indeed, in experimental studies, VO can increase the levels of the brain-derived neurotrophic factor (BDNF), promoting neurogenesis, dendritic branching and dendrite spine maturation and forming functional synapses by mitochondrial support in the hippocampus dentate gyrus. Interestingly, this action was detected only after 1 day of treatment with VO, in contrast to fluoxetine, which induced similar effects after 7 days. In addition, VO has proved to induce maturation of immature neurons.

### Table 1. Multimodal mechanism of action of VO.

| Target | Effect | Activity |
|--------|--------|----------|
| SERT inhibitor | Increase of 5-HT in the prefrontal cortex | Antidepressant activity |
| Full agonist 5-HT 1A Presynaptic autoreceptors | Acceleration of the receptor desensitisation | Reduction of the latency of action |
| Full agonist 5-HT 1A Postsynaptic receptors | Inhibition of the GABAergic interneurons \(+\) Release of Glu, NA, DO, AcH and Hist in the prefrontal cortex | Pro-cognitive activity |
| Partial agonist 5-HT 1B Presynaptic autoreceptors | Increase of 5-HT | Antidepressant activity Pro-cognitive activity |
| Partial agonist 5-HT 1B Postsynaptic receptors | Inhibition of the GABAergic interneurons \(+\) Release of Glu, NA, DO, AcH and Hist in the prefrontal cortex and hippocampus | Pro-cognitive activity |
| Antagonist 5-HT 1D Presynaptic autoreceptors | Increase of 5-HT | Improvement in Sleep |
| Antagonist 5-HT 3 Postsynaptic receptors | Inhibition of the GABAergic interneurons \(+\) Release of Glu, NA Ach in the prefrontal cortex and hippocampus | Pro-cognitive activity Improvement in sleep |
| Antagonist 5-HT 3 Postsynaptic receptors (Dorsal horn of the spinal cord) Full occupancy | Reduction of Hyperalgesia | Pain control |
| Antagonist 5-HT 7 Postsynaptic receptors (Dorsal horn of the spinal cord) 20% occupancy | Increase of Analgesia | Pain control |
| Antagonist 5-HT 7 Postsynaptic receptors | Inhibition of the GABAergic interneurons of the raphe nuclei \(+\) Increase of 5-HT, NA, Ach in the medial prefrontal cortex | Improvement in sleep |
| Increase of IL-4 | Regulator of the immune response in the brain Increase of BDNF | Anti-inflammatory phenotype differentiation of the macrophages of the microglia |
| Increase of BDNF | Brain neuroplasticity | Pro-cognitive activity |

5-HT: serotonin; AcH: acetylcholine; BDNF: brain derived neurotrophic factor; DA: dopamine; GABA: gamma-aminobutyric acid; Glu: glutamate; Hist: histamine; IL: interleukin; NA: noradrenaline; SERT: serotonin transporter; VO, vortioxetine.
by increasing dendritic length and the number of dendritic intersections in the dentate gyrus. All these actions work in a synergistic way, leading to an overall enhancement of brain performance, particularly important in elderly patients where cognitive impairment could be an aggravating factor for depression and CNP.

VO has also been demonstrated to improve the quality of sleep by enhancing non-REM sleep and increasing slow-wave sleep (through its agonism on the 5-HT1A and antagonism on the 5HT-3 receptors) and by suppressing REM sleep (through its antagonism on the 5HT-7 and 5HT-1D receptors). This effect should be considered carefully in the management of CNP where sleep disturbance is frequently reported.

**VO in pain modulation**

The mechanisms explaining how VO modulates pain are still not fully understood but it seems that the analgesic effect could be independent of its effect on depression and anxiety although the improvement in mood may potentially ameliorate the experience of pain and the ability to cope with pain.

Recently, in two experimental studies VO has demonstrated its efficacy in modulating pain in two models of CNP.

In the study of Zuena et al., VO venlafaxine and fluoxetine (all at 10 mg/kg, p.o.) were compared in modulation of pain in an established mouse model of NP.

VO has demonstrated a strong analgesic action in the chronic constriction injury model of NP, with an effect identical to that produced by venlafaxine, but different to that exhibited by fluoxetine. In detail, fluoxetine treatment in CCI mice had no effect on induced tactile allodynia on mice; instead, venlafaxine or VO caused a robust analgesia that was initially observed at day 7 and became substantial at day 12 of the treatment.

Subsequently, in the study of Micov et al., VO induced analgesia in an oxaliplatin-induced neuropathy model in mice. The drug (at dosage of 1–10 mg/kg, p.o.) reduced significantly, in a dose-dependent manner, not only the mechanical allodynia in the von Frey test and the cold allodynia in the acetone test but also depressive-like behaviour in the forced swimming test in the tested mice. In this study, the analgesia produced by VO was found to be similar to that produced by duloxetine (at dosage of 1–15 mg/kg, p.o.), despite the difference in the mechanism of action between these two drugs. In detail, the maximum effect of VO was achieved from the 7th to 10th day after oxaliplatin injection and the effects were 60%, 71% and 88% for doses of 1, 5 and 10 mg/kg, respectively. The maximum effect of duloxetine was achieved from day 7 to day 14 after oxaliplatin injection. The effects were 40%, 62% and 81% for doses of 1, 5 and 15 mg/kg, respectively.

Despite the limited number of studies in this field, these results have suggested that VO could potentially be used in the prevention and treatment of chemotherapy-induced neuropathy, and also of other types of CNP, considering that, until now, duloxetine is currently the only drug of choice for the treatment of this condition.

VO exhibits several actions that might explain its role in pain modulation. First, the blocking of SERT results in the up-regulation of biogenic amine neurotransmitters such as 5-HT and noradrenalin in the synaptic cleft of the central and peripheral nervous system, which can modulate pain transmission. Secondly, the direct modulation of receptor activity contributes to the allodynic action of the drug.

Therefore, the increase in the 5-HT level seems to be a consequence of the SERT inhibition empowered by the 5-HT3 receptor antagonism and 5-HT1A receptor stimulation, as each of these actions produces a greater 5-HT elevation than SERT inhibition alone. In addition, in vivo studies on rats have demonstrated that the antagonism of the 5-HT3 receptors increases the noradrenalin levels in the hippocampus and that the agonism of the 5-HT1A receptors increases the noradrenalin levels in the hypothalamus and hippocampus.

The increase of these neurotransmitters, especially 5-HT, and the downregulation and desensitisation of the pre- and post-synaptic receptors of the spinal dorsal horns over time contribute to a reduction in the ascending pain signals to the central nervous system (CNS). Less time is needed for the desensitisation for VO compared with the SSRIs and SNRIs on account of its unique selective agonism toward the serotonergic receptor 5-HT1A.
In addition, the synergic increase of the levels of 5-HT, noradrenaline and dopamine in the CNS contribute to strengthening the function of the descending inhibitory system, which can regulate the ascending nociceptive pathway.76,77

Indeed, the descending inhibitory fibres that originate in the brainstem and terminate in the spinal dorsal horn can be either inhibitory or facilitatory of pain; these fibres suppress pain neurotransmission working through the release of 5-HT and noradrenaline.78 Therefore a dysfunction of these systems can cause a dysfunction of the descending 5-HT and noradrenaline anti-nociceptive pathways and can exacerbate the chronic pain condition.79

In condition of CNP, the serotonergic pathway descending from the lower brainstem to the dorsal horn of the spinal cord are hyperalgesic and this effect is mediated by the activation of 5HT3 receptors.80 In detail, the top-down inhibitory control of pain is mediated by the 5-HT effect on the receptor subtypes that are preferentially activated, particularly the 5-HT induced analgesia mediated by the 5-HT7 receptors and the hyperalgesia mediated by 5-HT3.69 Indeed, in rodents with peripheral neuropathy, the administration of the 5-HT3 antagonist resulted in a pain-suppressing effect, alleviating mechanical hypersensitivity and evokes the potential of the dorsal horn neurons in rats with peripheral nerve injury.23,84,85 However, the antagonism of the 5-HT1D receptors by VO is still much debated, considering that the role of these receptors in CNP modulation is rather inhibitory.83

CNP is associated with structural and functional changes in the brain with an impaired connectivity of the hippocampus, amygdala and cortex.86 Specifically, the hippocampus is a part of the brain limbic region critically implicated in modulating the emotional component of pain and is also particularly vulnerable to stress – its atrophy being a common finding in chronic pain and mood disorders.87

In this context, the increase of the synaptic neuroplasticity of the brain induced by VO could play a pivotal role by reverting these brain alterations through neurogenesis.88 Moreover, VO increases the level of the BDNF, restoring lost neurons, and potentially contributes to recovery from chronic pain.62,89–92

A growing body of evidence supports the hypothesis that an increased level of pro-inflammatory cytokines is crucial in the development of pathological pain; in experimental studies VO has been demonstrated to exhibit immunomodulatory properties, antioxidant activity and intrinsic anti-inflammatory effects.93

This anti-inflammatory profile of VO is superior when compared with amitriptyline and S-citalopram.94 Therefore, the analgesia induced by VO may also be explained in terms of a decrease of the neuroinflammation; this effect is mediated by modulation of microglia cells of the brain.95

Indeed, the involvement of the microglia and astrocytes in some brain regions including the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens has been considered in the pathogenesis of CNP.95–98
In normal circumstances, the microglia cells are resident inactive macrophages of the CNS (inactive or resting microglia) but after stress exposure and in CNP conditions the signalling between the microglia cells, astrocytes and neural cells is modified. Indeed, these nociceptive neurons can activate some subtype cells of the microglia (the M1 inflammatory phenotype) through the release of ATP chemokine and fractalkine.95,97

In turn, the activated microglial cells (M1) release proinflammatory cytokines such as tumour necrosis factor α (TNF α) and interleukin 1 β (IL-1β), which can contribute to the neuroinflammatory process, neuronal apoptosis and central sensitisation in chronic pain.99–101

Similarly, the activation of astrocytes mediates the neuroinflammation, induces neuronal hyperexcitability and plays a role in the maintenance of a status of chronic pain.97

In contrast, the activation of another subtype of the microglia cells (the M2 anti-inflammatory phenotype) and astrocytes can promote an anti-inflammatory response, causing tissue repair and angiogenesis.102

In this context, the modulation of communication among the microglia cells, astrocytes and neural cells with a concomitant shift of microglia from the M1 to the M2 phenotype may hold a key role in the improvement in pain perception, particularly in the hippocampus region.103,104

Recent experimental studies, have shown that VO could have a selective role in the maintenance of an anti-inflammatory status through the inhibition of the subtype of activated microglia (M1 phenotype) driving the shift versus an M2 anti-inflammatory phenotype, via 5-HT2b and 5-HT7 receptors, blocking neuroinflammation, enhancing neurogenesis and neuroplasticity.93,105

Dosage
VO is available as 5 mg, 10 mg and 20 mg tablets and drops. Doses of 5–20 mg were found to be effective, with doses of 20 mg exhibiting a greater clinical response. However, a lack of effectiveness was found at lower doses of 2.5–5 mg.29

The recommended starting dose of VO is 10 mg daily. However, dose adjustment should be considered on a patient-by-patient basis until a clinical remission of the pain and an improvement of the mood disorders is achieved. Indeed, the progressive up-titration of the dosage until 20 mg daily was proven to be efficacious and safe, as also suggested by several studies.111 Nevertheless, the EU health authorities recommend initiating treatment in the elderly with a daily dose of 5 mg (and advise caution when prescribing VO at a dose of 10 mg/day), due to the fact that exposure to VO may increase by up to 27% in healthy volunteers aged 65 years as compared with those aged 45 years, who had received multiple doses of 10 mg/day.112

Pharmacokinetics
The pharmacokinetic properties of VO have been studied in mice, rats, dogs, and in human subjects.30,112–116

In humans, the absolute bioavailability of VO, determined after intravenous and oral administrations to the same volunteers, was high (up to 75%) and independent of food intake.117

VO shows a linear, dose-proportional and time-independent pharmacokinetics at doses from 2.5 mg to 75 mg.118 It has an extensive volume of distribution as the plasma protein binding is 80–90%. It takes 3–16 h to attain maximum plasma concentration, with a terminal half-life of approximately 60–70 h, and a steady-state concentration in the plasma maintained for up to 2 weeks after drug administration.112

VO is metabolised extensively in the liver, primarily by several cytochrome CYP450 enzymes (including CYP2D6, CYP3A4/5, CYP2C9,
CYP2C19, CYP2A6, CYP2C8 and CYP2B6) with a subsequent glucuronic acid conjugation in pharmacologically inactive metabolites. In detail, CYP2D6 is the primary enzyme catalysing the metabolism of VO to its major metabolite (Lu AA34443), which is inactive. A second metabolite (Lu AA39835) is equipotent to VO as an inhibitor of human 5-HT transporter, but its concentration is much lower than that of the parent compound in plasma (i.e. metabolic ratio $\leq 0.04$), and it is not expected to have effects on the CNS based on a nonclinical pharmacology study. Therefore, the clinical activity of the drug can be attributed solely to the parent compound. On account of its inability to inhibit or induce P450 enzymes, VO appears to have a relatively safe drug–drug interaction profile.

Intrinsic factors, such as age, sex, race, body size, and hepatic and renal impairment, had no significant effects on VO exposure, suggesting that no dosing adjustment is required for this drug.

However, as VO is a serotonergic agent, it should be used carefully in combination with other serotonergic drugs. In particular, VO being a substrate for the cytochrome P450 enzyme CYP2D6 requires an adjustment of the dose when given in combination with CYP2D6 inhibitors (buproprion, fluoxetine or paroxetine). In turn, co-administration with robust CYP inducers (carbamazepine, phenytoin or rifampicin) requires an increased dose of VO.

In addition, the co-administration of ketoconazole 400 mg/daily (CYP3A4/5 inhibitor) or fluconazole 200 mg/daily (CYP2C9, CYP2C19, and CYP3A4/5 inhibitor) with VO (10 mg/daily) increased the AUC$_{(0-t)}$ of the drug by 30 and 46%, respectively. However, given the modest increases, these findings were not considered clinically meaningful.

Instead, the co-administration of ethanol, aspirin or omeprazole (CYP2C19 inhibitors) had no effect on exposure to VO.

**Safety, tolerability and drop-out**

VO showed a favourable profile, both in short- and long-term clinical placebo-controlled studies, in terms of safety and tolerability at dosages of 5–20 mg. The most common adverse drug reactions (ADRs), reported in 5% of subjects, were, in order of incidence, nausea, headache, diarrhoea and dry mouth. It is well established that the most common ADR is nausea (affecting more than 1 in 10 people; 20.9/31.2%), generally with a mild or moderate severity. It has not been clarified how VO can induce this side effect, although nausea might be related to the serotonergic hyperactivation as consequence of the increase availability of 5-HT in the gastrointestinal tract and in the CNS or possibly to the genetic polymorphism of the monoamine oxidase A (MAOA-VNTR) which may influence the individual’s susceptibility toward this side effect. Generally, the nausea is usually transient, dose-related and more common in women and during the first week of treatment.

The incidence of haemorrhage in a short-term clinical study with a dose range of 10–20 mg/day was low, and similar between VO (1.7%) and placebo (1.2%) participants.

The good tolerability of VO has been demonstrated on account of the fact that no effects have been reported in the biochemical parameters, vital signs, body weight, heart rate, blood pressure or electrocardiogram parameters, including the QTcF interval. This aspect represents an important advantage of this drug, for both young and elderly patients, as it signifies an avoidance of any negative metabolic effects and related reasons for treatment discontinuation.

The incidence of sexual dysfunction was lower in relation to treatment with VO as compared with treatment with SSRIs. Interestingly, in a recent study this ADR was reported to be higher with a low dose of VO, namely 2.5 mg, compared with a 5 mg dose, with a higher incidence in men. In addition, switching patients already experiencing sexual dysfunction from previous antidepressants to VO led to a reduction in the incidence of sexual impairment while maintaining an adequate management of depressive symptoms.

On the other hand, VO has not been tested sufficiently in pregnant human subjects, but in animal studies decreased foetal weight and delayed ossification have been reported.

The sudden discontinuation of VO after 2 weeks of treatment showed no clinically significant withdrawal effects as compared with placebo (4.5–7.8% in the VO group versus 3.6% in the placebo-treated group).
Overall, VO has been demonstrated to be one of the most tolerable antidepressants, associated with the lowest rate of dropout, as suggested by a recent systematic review performed by Cipriani et al.\textsuperscript{130}

**Clinical use**

**VO in the treatment of major depressive disorder**

The efficacy of VO in the treatment of major depressive disorder (MDD) has been established in several short-term (6, 8 and 12 weeks) RCTs in adults at a dose range of 5–20 mg, where the higher doses were associated with increasing clinical effects.\textsuperscript{131–140}

In RCTs in which active comparators were used, VO showed a significant superiority when compared with agomelatine and non-inferiority when compared with venlafaxine,\textsuperscript{132,141} escitalopram or duloxetine.\textsuperscript{43,131,142,143} The efficacy of VO has been confirmed also in a long-term clinical trial (52 weeks).\textsuperscript{144,145}

Moreover, in patients who had exhibited an inadequate response to SSRIs or SNRIs before switching to VO,\textsuperscript{146} this drug proved to be significantly superior to agomelatine in terms of reducing depressive symptoms in SSRI non-responders,\textsuperscript{147} although not in SNRI patients.\textsuperscript{141}

A recent systematic review and network meta-analysis, which compared the efficacy and acceptability of 21 antidepressant drugs in the treatment of MDD, has shown that VO, together with agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine and venlafaxine, was more effective than other ADs.\textsuperscript{130} These results are in line with previous meta-regression analyses performed by Llorca et al.\textsuperscript{121} and confirmed by Chen et al.\textsuperscript{148} Instead, in the study of Wagner et al., VO showed a similar efficacy to that of levomilnacipran and vilazodone.\textsuperscript{149}

In addition, VO showed the best tolerability profile,\textsuperscript{29,150} especially in patients of 65 years or older previously treated with SNRIs, and SSRIs, with a statistically lower number of overall ADRs compared with VO.\textsuperscript{151} However, in a systematic review performed by Li et al.,\textsuperscript{152} VO was found to be less effective than duloxetine, even though patients treated with VO did not develop ADRs.

Despite the uncertainty about the choice of specific drug for the treatment of MDD, it is important to consider that patients treated with VO displayed an improvement in terms of a reduction of depressive symptoms, namely a full functional recovery and restoration of function in several domains of daily life activities after only 8 weeks of treatment, unlike treatment with placebo or duloxetine.\textsuperscript{153} This result was confirmed by a meta-analysis of an elderly population where treatment with VO (15–20 mg) resulted in a significant improvement in the self-perception of physical health mental health and energy, and subsequently of quality-of-life, in MDD patients, compared with treatment with a placebo.\textsuperscript{154}

**VO in the treatment of anxiety**

The efficacy of VO in the treatment of generalised anxiety disorders (GAD) is still debated.

In the systematic review of Pae et al.,\textsuperscript{155} the authors suggest that VO may have a potential benefit in the treatment of GAD since VO was found to be more effective than placebo, particularly in patients with a severe form of GAD and with higher scores in the Hamilton anxiety rating scale (HAM-A) test.\textsuperscript{156}

However, in a recent systematic review and network meta-analysis of double-blind RCTs performed by Kong et al.,\textsuperscript{157} despite the tolerability of VO, its efficacy was comparable with that of placebo while the remission rate of agomelatine, duloxetine, escitalopram, paroxetine, quetiapine and venlafaxine was superior to that of placebo.

In relation to panic disorders and social disorders, preliminary results have shown a potential advantage in terms of efficacy in a long-term treatment with VO, despite no evidence about the optimal length of treatment and dosage having been reported.\textsuperscript{158–160}

**VO in the treatment of cognitive impairment**

Several RCTs have demonstrated the efficacy of VO in terms of enhancing cognitive performance in patients with MDD – an effect considered independently of any alleviation of depressive symptoms. Indeed, the cognitive benefits of VO rely on its action on receptor activity, in particular 5-HT3 receptor antagonism.\textsuperscript{143,161–164}

At a dosage of 10–20 mg, VO was superior to placebo in improving attention, memory, learning, processing speed and executive functions, especially in elderly populations.\textsuperscript{143}
These results were confirmed by a recent systematic review by Blumberg et al.,165 where only VO and bupropion have demonstrated pro-cognitive effects in patients with MDD whereas no effects were reported for tricyclic ADs, SSRIs and SNRIs.

Moreover, in a recent short-term (8 weeks) placebo controlled RCT, VO seemed to be efficacious both in monotherapy or as an adjunctive treatment to SSRI, also in the treatment of residual cognitive symptoms in patients affected by MDD.51

**VO in the treatment of sleep disturbances**

VO showed efficacy in the treatment of sleep disturbance in preliminary results and in open label studies at a dosage of 10–20mg.166 Indeed, VO improved sleep quality, leading to a reduction in the scores of the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale and Insomnia Severity Index already after 8 weeks of treatment.166–168

Moreover, Wilson et al. analysed the sleep architecture in 24 healthy young men treated with VO (20 mg), VO (40 mg), paroxetine (20 mg) or a placebo.169 All three active treatments significantly increased rapid eye movement (REM) onset latency and decreased the time spent in REM sleep.

**VO in the treatment of CNP**

Recently, in two pilot clinical studies, Adamo et al. tested VO in a sample of patients affected by chronic neuropathic orofacial pain (CNOP) with encouraging results, suggesting a new possibility in the management of these patients.111,168 Indeed, VO demonstrated efficacy in the relief of pain, anxiety, depression and sleep disturbance, improving the quality-of-life of the patients.111,168

No drug–drug interactions or side effects, such as QTc prolongation, sexual dysfunction or weight gain, were reported in these studies, in line with the findings from 11 double-blind RCTs on MDD.170

These results were further confirmed in a long-term (12 months) RCT on 150 patients, where the same authors compared VO with four of the most frequently prescribed ADs in the treatment of CNOP: paroxetine, sertraline, escitalopram and duloxetine.111 In this study, VO showed a faster-acting antidepressant activity and pain control compared with SSRIs and SNRIs.111

In detail, VO and paroxetine showed the best effectiveness in reducing pain intensity, evaluated by the visual analogic scale (VAS), after 1 year of treatment (median scores at T0 were 10.0 and decreased to 0 after 12 months) compared with other antidepressants (sertraline, escitalopram, duloxetine) whose median scores after 12 months ranged from 1.0 to 3.0. Moreover, VO was the most efficacious in controlling pain quality evaluated by the total pain rating index (T-PRI) as the median scores dropped from 22.0 to 2.0 after 1 year of treatment, while all the others were able to reduce pain quality from 18.0–22.00 to 4.5–9.0.

In addition, VO presented the highest rate of clinical response and remission, and the best acceptability by the patients, safety profile and tolerability, compared with the other four ADs.111 However, the authors revealed several differences between VO and the other ADs. Indeed, despite the fact that the acceptability of the treatment was good for all the drugs because no drop-out was reported before the sixth month, the patients who received VO were more enthusiastic about starting the treatment on account of its known pro-cognitive effect.111 In addition, in long-term analyses, although all the ADs showed a reduction in scores for pain, anxiety and depression, only VO showed any achievement in terms of clinical response and clinical remission, with a functional recovery in 96.6% and 83.3% of patients after 6 and 12 months of treatment, respectively.111 In addition, only 10% of patients treated with VO reported any side effects, in fact only nausea, and in most cases this resolved spontaneously after 2 weeks. However, abdominal pain, QTc prolongation, somnolence and sexual dysfunction were reported in treatment with other ADs.111

**Implications for the clinical care of CNP**

Currently, ADs such as duloxetine, venlafaxine and amitriptyline are considered the gold standard drugs in the treatment of various pain syndromes, including CNOP, fibromyalgia, migraine, functional abdominal pain and chemotherapy-induced neuropathy, on account of their efficacy in pain management, especially in patients with a psychiatric comorbidity.130,171 Despite the utility of these drugs, patients frequently discontinue...
treatment due to the occurrence of ADRs – a factor that may influence the choice of a drug for a specific patient.\textsuperscript{18} Therefore, VO could represent an important innovative option for the treatment of CNP and could be considered as the first line of treatment on account of its safety and tolerability profile, especially in elderly patients with cognitive impairment.

**Conclusions**

The management of CNP has become of the utmost importance in primary care due to the high prevalence of this disease in the general population and to the consequent increased demand for treatment. The frequent association of CNP with anxiety, depression and sleep disturbance has led clinicians to choose therapeutic strategies aimed not only at relieving the pain but also at treating the coexisting psychiatric comorbidities in order to provide a comprehensive management and therefore enhanced outcomes.\textsuperscript{5}

In this regard, VO is increasingly being considered as a treatment option. It is a novel drug that has proved to be well tolerated and effective in patients with CNOP in comparison with other ADs. In particular, VO has shown promising preliminary results in the treatment of CNOP and has therefore been suggested as a new frontier in the management not only of this disease but potentially of other chronic pain conditions. The use of VO presents several beneficial effects, especially in middle-aged or older patients, in whom VO improves several cognitive functions, along with providing a safe profile, good tolerability and lower latency of action.

Clinicians may choose to use VO (up to 20 mg/daily) either as a first line therapy or in the treatment of patients with an unsatisfactory response to other ADs or report the occurrence of ADRs. The treatment should be continued over the long term until the achievement of a clinical remission or response and a return to normal daily functioning, as suggested by a reduction in mood disorders, at least for 12 months because an early discontinuation of the drug may increase the risk of relapse and recurrence.\textsuperscript{172} A careful tapering is recommended when remission has been achieved to avoid any withdrawal symptoms or a relapse of the disease. In patients who report nausea as a side effect and in non-responder cases, another AD may be considered.\textsuperscript{111,168}

**Author contributions**

DA: conceptualisation; EC: methodology; NC: software; DA, MDM: validation; EC, NC: formal analysis; GP, EC: investigation; GP, DA: resources; GP, NC: data curation; DA, NC: writing – original draft preparation; DA, MDM: writing – review and editing; MDM: visualisation; DA, MDM: supervision. All authors contributed to the work and are familiar with the primary data; each has read the final version of the manuscript and approved its content. All the authors have agreed to have their name added to the paper.

**Conflict of interest statement**

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**References**

1. Sá KN, Moreira L, Baptista AF, \textit{et al.} Prevalence of chronic pain in developing countries: systematic review and meta-analysis. \textit{Pain Rep} 2019; 4: e779.

2. McWilliams DF and Walsh DA. Pain mechanisms in rheumatoid arthritis. \textit{Clin Exp Rheumatol} 2017; 35 Suppl 107: 94–101.

3. Alles SRA and Smith PA. Etiology and pharmacology of neuropathic pain. \textit{Pharmacol Rev} 2018; 70: 315–347.

4. IASP Taxonomy. (2011). International Association for the study of pain. \textit{IASP Publications}, http://www.iasp-pain.org/
5. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nat Rev Dis Primers* 2017; 3: 17002. Published 2017 Feb 16.

6. Yalcin I, Barthas F and Barrot M. Emotional consequences of neuropathic pain: insight from preclinical studies. *Neurosci Biobehav Rev* 2014; 47: 154–164.

7. Torta R, Ieraci V and Zizzi F. A review of the emotional aspects of neuropathic pain: from comorbidity to co-pathogenesis. *Pain Ther* 2017; 6: 11–17.

8. Nicholson B and Verma S. Comorbidities in chronic neuropathic pain. *Pain Med* 2004; 5: S9–S27.

9. Radat F, Margot-Duclot A and Attal N. Psychiatric co-morbidities in patients with chronic peripheral neuropathic pain: a multicentre cohort study. *Eur J Pain* 2013; 17: 1547–1557.

10. Humo M, Lu H and Yalcin I. The molecular neurobiology of chronic pain-induced depression. *Cell Tissue Res* 2019; 377: 21–43.

11. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162–173.

12. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17: 1113–e88.

13. Więdłocha M, Marcinowicz P, Krupa R, et al. Effect of antidepressant treatment on peripheral inflammation markers: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 80: 217–226.

14. Wattiez AS, Dupuis A, Privat AM, et al. Disruption of 5-HT 2A -PDZ protein interaction differently affects the analgesic efficacy of SSRI, SNRI and TCA in the treatment of traumatic neuropathic pain in rats. *Neuropharmacol* 2017; 125: 308–318.

15. Dupuis A, Wattiez AS, Pinguet J, et al. Increasing spinal 5-HT 2A receptor responsiveness mediates anti-allodynic effect and potentiates fluoxetine efficacy in neuropathic rats. Evidence for GABA release. *Pharmacol Res* 2017; 118: 93–103.

16. Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; 42: 135–144.

17. Giannopoulos S, Kosmidou M, Sarmas I, et al. Patient compliance with SSRIs and gabapentin in painful diabetic neuropathy. *Clin J Pain* 2007; 23: 267–269.

18. Wang SM, Han C, Bahk WM, et al. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Med J* 2018; 54: 101–112.

19. Urits I, Peck J, Orhurhu MS, et al. Off-label antidepressant use for treatment and management of chronic pain: evolving understanding and comprehensive review. *Curr Pain Headache Rep* 2019; 23: 66.

20. Food and Drug Administration. Brintellix™ (vortioxetine) tablets for oral use. Full prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf (2013, accessed 13 February 2021).

21. European Medicines Agency. EPAR brintellix product information. Annex I. Summary of product characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002717/WC500159449.pdf (2014, accessed 13 Feruary 2021).

22. WHO Collaborating Centre for Drug Statistics Methodology. Oslo: ATC classification index with DDDs, https://www.whocc.no/atc/ 2019.

23. Sowa-Kućma M, Pańczyszyn-Trzecik P, Misztak P, et al. Vortioxetine: a review of the pharmacology and clinical profile of the novel antidepressant. *Pharmacol Rep* 2017; 69: 595–601.

24. Sanchez C, Asin KE and Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther* 2015; 145: 43–57.

25. Riga MS, Sánchez C, Celada P, et al. Involvement of 5-HT 3 receptors in the action of vortioxetine in rat brain: focus on glutamatergic and GABAergic neurotransmission. *Neuropharmacol* 2016; 108: 73–81.

26. Frampton JE. Vortioxetine: a review in cognitive dysfunction in depression. *Drugs* 2016; 76: 1675–1682.
29. Gonda X, Sharma SR and Tarazi FI. Vortioxetine: a novel antidepressant for the treatment of major depressive disorder. *Expert Opin Drug Discov* 2019; 14: 81–89.

30. Pehrson AL, Hillhouse TM, Haddjeri N, et al. Task- and treatment length-dependent effects of vortioxetine on scopolamine-induced cognitive dysfunction and Hippocampal extracellular acetylcholine in rats. *J Pharmacol Exp Ther* 2016; 358: 472–482.

31. Mørk A, Pehrson A, Brennum LT, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther* 2012; 340: 666–675.

32. Lecours M, El Mansari M and Blier P. P.2.b.015 electrophysiological effects of the multimodal antidepressant Lu AA21004 on serotonin transmission in the rat hippocampus. *Eur Neuropsychopharmacol* 2012; 22: S249.

33. Bonaventure P, Dugovic C, Kramer M, et al. Translational evaluation of JNJ-18038683, a 5-hydroxytryptamine type 7 receptor antagonist, on rapid eye movement sleep and in major depressive disorder. *J Pharmacol Exp Ther* 2012; 342: 429–440.

34. Stenkrona P, Halldin C and Lundberg J. 5-HTT and 5-HT1A receptor occupancy of the novel substance vortioxetine (Lu AA21004). A PET study in control subjects. *Eur Neuropsychopharmacol* 2013; 23: 1190–1198.

35. Vahid-Ansari F, Zhang M, Zahrai A, et al. Overcoming resistance to selective serotonin reuptake inhibitors: targeting serotonin, serotonin-1A receptors and adult neuroplasticity. *Front Neurosci* 2019; 13: 404.

36. Okada M, Okubo R and Fukuyama K. Vortioxetine subchronically activates serotonergic transmission via desensitization of Serotonin 5-HT1A receptor with 5-HT3 receptor inhibition in rats. *Int J Mol Sci* 2019; 20: 6235.

37. El Mansari M, Lecours M and Blier P. Effects of acute and sustained administration of vortioxetine on the serotonin system in the hippocampus: electrophysiological studies in the rat brain. *Psychopharmacology (Berl)* 2015; 232: 2343–2352.

38. Okubo R, Hasegawa T, Fukuyama K, et al. Current limitations and candidate potential of 5-HT7 receptor antagonism in psychiatric pharmacotherapy. *Front Psychiatry* 2021; 12: 623684.

39. du Jardin KG, Jensen JB, Sanchez C, et al. Vortioxetine dose-dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: a potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. *Eur Neuropsychopharmacol* 2014; 24: 160–171.

40. Jensen JB, du Jardin KG, Song D, et al. Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: evidence for direct 5-HT receptor modulation. *Eur Neuropsychopharmacol* 2014; 24: 148–159.

41. Wallace A, Pehrson AL, Sánchez C, et al. Vortioxetine restores reversal learning impaired by 5-HT depletion or chronic intermittent cold stress in rats. *Int J Neuropsychopharmacol* 2014; 17: 1695–1706.

42. Jiang LX, Huang GD, Su F, et al. Vortioxetine administration attenuates cognitive and synaptic deficits in 5×FAD mice. *Psychopharmacology (Berl)* 2020; 237: 1233–1243.

43. McIntyre RS, Lophaven S and Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 2014; 17: 1557–1567.

44. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl)* 2015; 232: 2061–2070.

45. McIntyre RS, Harrison J, Loft H, et al. The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. *Int J Neuropsychopharmacol* 2016; 19: w055.

46. McIntyre RS, Florea I, Tonnoir B, et al. Efficacy of vortioxetine on cognitive functioning in working patients with major depressive disorder. *J Clin Psychiatry* 2017; 78: 115–121.

47. Baune BT, Brignone M and Larsen KG. A network meta-analysis comparing effects of various antidepressant classes on the digit symbol substitution test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder. *Int J Neuropsychopharmacol* 2018; 21: 97–107.

48. Vieta E, Sluth LB and Olsen CK. The effects of vortioxetine on cognitive dysfunction in patients with inadequate response to current antidepressants in major depressive disorder: a short-term, randomized, double-blind, exploratory study versus escitalopram. *J Affect Disord* 2018; 227: 803–809.
49. Freeman MP, Cheng LJ, Moustafa D, et al. Vortioxetine for major depressive disorder, vasomotor, and cognitive symptoms associated with the menopausal transition. Ann Clin Psychiatry 2017; 29: 249–257.

50. Smith J, Browning M, Conen S, et al. Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. Mol Psychiatry 2018; 23: 1127–1133.

51. Areberg J, Luntang-Jensen M, Søgaard B, et al. Occupancy of the serotonin transporter after administration of Lu AA21004 and its relation to plasma concentration in healthy subjects. Basic Clin Pharmacol Toxicol 2012; 110: 401–404.

52. Nierenberg AA, Loft H and Olsen CK. Treatment effects on residual cognitive symptoms among partially or fully remitted patients with major depressive disorder: a randomized, double-blinded, exploratory study with vortioxetine. J Affect Disord 2019; 250: 35–42.

53. Rosenblat JD, Kakar R and McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 2016; 19: v082.

54. Levada OA and Troyan AS. Cognitive-functional relationships in major depressive disorder: crucial data from a Ukrainian open-label study of vortioxetine versus escitalopram. J Affect Disord 2019; 250: 114–122.

55. Bennabi D, Haffen E and Van Waes V. Vortioxetine for cognitive enhancement in major depression: from animal models to clinical research. Front Psychiatry 2019; 10: 771. Published 2019 Nov 6.

56. Kugathasan P, Waller J, Westrich L, et al. In vivo and in vitro effects of vortioxetine on molecules associated with neuroplasticity. J Psychopharmacol 2017; 31: 365–376.

57. Smagin GN, Song D, Budac DP, et al. Histamine may contribute to vortioxetine's procognitive effects; possibly through an orexigenic mechanism. Prog Neuropsychopharmacol Biol Psychiatry 2016; 68: 25–30.

58. Bang-Andersen B, Ruhland T, Jørgensen M, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem 2011; 54: 3206–3221.

59. Diaz-Mataix L, Scorza MC, Bortolozzi A, et al. Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. J Neurosci 2005; 25: 10831–10843.

60. Micheli L, Ceccarelli M, D’Andrea G, et al. Depression and adult neurogenesis: positive effects of the antidepressant fluoxetine and of physical exercise. Brain Res Bull 2018; 143: 181–193.

61. Mateus-Pinheiro A, Pinto L, Bessa JM, et al. Sustained remission from depressive-like behavior depends on hippocampal neurogenesis. Transl Psychiatry 2013; 3: e210.

62. Lu Y, Ho CS, McIntyre RS, et al. Effects of vortioxetine and fluoxetine on the level of brain derived neurotrophic factors (BDNF) in the hippocampus of chronic unpredictable mild stress-induced depressive rats. Brain Res Bull 2018; 142: 1–7.

63. Waller JA, Chen F and Sánchez C. Vortioxetine promotes maturation of dendritic spines in vitro: a comparative study in hippocampal cultures. Neuropsychopharmacol 2016; 103: 143–154.

64. Bétry C, Pehrson AL, Étiévant A, et al. The rapid recovery of 5-HT cell firing induced by the antidepressant vortioxetine involves 5-HT3 receptor antagonism. Int J Neuropsychopharmacol 2013; 16: 1115–1127.

65. Guilloux JP, Mendez-David I, Pehrson A, et al. Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and neurogenesis outcomes in mice. Neuropsychopharmacol 2013; 73: 147–159.

66. Adamo D, Sardella A, Varoni E, et al. The association between burning mouth syndrome and sleep disturbance: a case-control multicentre study. Oral Dis 2018; 24: 638–649.

67. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. Placebo in patients with painful diabetic neuropathy. Pain 2005; 116: 109–118.

68. Papandreou C, Skapinakis P, Giannakis D, et al. Antidepressant drugs for chronic urological pelvic pain: an evidence-based review. Adv Urol 2009; 2009: 1–9.

69. Zuena AR, Maftei D, Alemà GS, et al. Multimodal antidepressant vortioxetine causes analgesia in a mouse model of chronic neuropathic pain. Mol Pain 2018; 14: 1–9. DOI: 10.1177/1744806918808987.

70. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors
and pathways mediate therapeutic effects and side effects. *J Affect Disord* 1998; 51: 215–235.

71. Pacher P and Kecskemeti V. Trends in the development of new antidepressants. Is there a light at the end of the tunnel? *Curr Med Chem* 2004; 11: 925–943.

72. Fanburg BL and Lee SL. A role for the serotonin transporter in hypoxia-induced pulmonary hypertension. *J Pharmacol Exp Ther* 1995; 272: 1044–1051.

73. Matsumoto M, Yoshioka M, Togashi H, et al. Modulation of norepinephrine release by serotonergic receptors in the rat hippocampus as measured by in vivo microdialysis. *J Pharmacol Exp Ther* 1995; 272: 1044–1051.

74. Suwabe A, Kubota M, Niwa M, et al. Effect of a 5-HT1A receptor agonist, flesinoxan, on the extracellular noradrenaline level in the hippocampus and on the locomotor activity of rats. *Brain Res* 2000; 858: 393–401.

75. Chen M, Hoshino H, Saito S, et al. Spinal dopaminergic involvement in the antihyperalgesic effect of antidepressants in a rat model of neuropathic pain. *Neurosci Lett* 2000; 282: 319–325.

76. Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. *Int J Mol Sci* 2017; 18: 2483.

77. Pertoavaara A and Almeida A. Chapter 13 descending inhibitory systems. *Handb Clin Neurol* 2006; 81: 179–192.

78. Porreca F, Ossipov MH and Gebhart GF. Chronic pain and medullary descending facilitation. *Trends Neurosci* 2002; 25: 319–325.

79. Lv Q, Wu F, Gan X, et al. The involvement of descending pain inhibitory system in electroacupuncture-induced analgesia. *Front Integr Neurosci* 2019; 13: 38.

80. Ossipov MH, Dusser GO and Porreca F. Central modulation of pain. *J Clin Investig* 2010; 120: 3779–3787.

81. Nasirinezhad F, Hosseini M, Karami Z, et al. Spinal 5-HT1 receptor mediates nociceptive effect on central neuropathic pain; possible therapeutic role for tropisetron. *J Spinal Cord Med* 2016; 39: 212–219.

82. Leiser SC, Pehrson AL, Robichaud PJ, et al. Multimodal antidepressant vortioxetine increases frontal cortical oscillations unlike escitalopram and duloxetine: a quantitative EEG study in rats. *Br J Pharmacol* 2014; 171: 4255–4272.

83. Viguier F, Michot B, Hamon M, et al. Multiple roles of serotonin in pain control mechanisms: implications of 5-HT7 and other 5-HT receptor types. *Eur J Pharmacol* 2013; 716: 8–16.

84. Avila-Rojas SH, Velázquez-Lagunas I, Salinas-Abarca AB, et al. Role of spinal 5-HT3A and 5-HT1A/1D receptors in neuropathic pain induced by spinal nerve ligation in rats. *Brain Res* 2015; 1622: 377–385.

85. Sagalajev B, Bourbina N, Beloushko E, et al. Bidirectional amygdaloid control of neuropathic hypersensitivity mediated by descending serotonergic pathways acting on spinal 5-HT3 and 5-HT1A receptors. *Behav Brain Res* 2015; 282: 14–24.

86. Yang S and Chang MC. Chronic pain: structural and functional changes in brain structures and associated negative affective states. *Int J Mol Sci* 2019; 20: 3130.

87. Dhikav V and Anand K. Hippocampus in health and disease: an overview. *Ann Indian Acad Neurol* 2012; 15: 239–246.

88. Horderbach R, Clark K, Moreau JL, et al. Enhanced long-term synaptic depression in an animal model of depression. *Biol Psychiatry* 2007; 62: 92–100.

89. Neto FL, Borges G, Torres-Sanchez S, et al. Neurotrophins role in depression neurobiology: a review of basic and clinical evidence. *Curr Neuropsychopharmacol* 2011; 9: 530–552.

90. Zhang H, Qian YL, Li C, et al. Brain-derived neurotrophic factor in the Mesolimbic reward circuitry mediates nociception in chronic neuropathic pain. *Biol Psychiatry* 2017; 82: 608–618.

91. Sun B, Lv Y, Xu H, et al. Effects of vortioxetine on depression model rats and expression of BDNF and Trk B in hippocampus. *Exp Ther Med* 2020; 20: 2895–2902.

92. Carta MG, Pala AN, Finco G, et al. Depression and cerebrovascular disease: could vortioxetine represent a valid treatment option? *Clin Pract Epidemiol Ment Health* 2015; 11: 144–149.

93. Talmon M, Rossi S, Pastore A, et al. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. *Br J Pharmacol* 2018; 175: 113–124.

94. Tomaz VDS, Chaves Filho AJM, Cordeiro RC, et al. Antidepressants of different classes cause distinct behavioral and brain pro- and anti-inflammatory changes in mice submitted to an inflammatory model of depression. *J Affect Disord* 2020; 268: 188–200.
95. Xu N, Tang XH, Pan W, et al. Spared nerve injury increases the expression of microglia M1 markers in the prefrontal cortex of rats and provokes depression-like behaviors. *Front Neurosci* 2017; 11: 209.

96. Gui WS, Wei X, Mai CL, et al. Interleukin-1β overproduction is a common cause for neuropathic pain, memory deficit, and depression following peripheral nerve injury in rodents. *Mol Pain* 2016; 12: 1–15. DOI: 10.1177/1744806916646784.

97. Taylor AMW, Mehrabani S, Liu S, et al. Topography of microglial activation in sensory- and affect-related brain regions in chronic pain. *J Neurosci Res* 2017; 95: 1330–1335.

98. Barcelon EE, Cho WH, Jun SB, et al. Brain microglial activation in chronic pain-associated affective disorder. *Front Neurosci* 2019; 13: 213.

99. Ji RR, Chamessian A and Zhang YQ. Pain regulation by non-neuronal cells and inflammation. *Science* 2016; 354: 572–577.

100. Rahimifard M, Maqbool F, Moenini-Nodeh S, et al. Targeting the TLR4 signaling pathway by polyphenols: a novel therapeutic strategy for neuroinflammation. *Aging Res Rev* 2017; 36: 11–19.

101. Hore Z and Denk F. Neuroimmune interactions in chronic pain: an interdisciplinary perspective. *Brain Behav Immun* 2019; 79: 56–62.

102. Cherry JD, Olschowka JA and O’Banion MK. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. *J Neuroinflammation* 2014; 11: 98.

103. Vanderwall AG and Milligan ED. Cytokines in pain: harnessing endogenous anti-inflammatory signaling for improved pain management. *Front Immunol* 2019; 10: 3009.

104. Alboni S, Benatti C, Colliva C, et al. Vortioxetine prevents lipopolysaccharide-induced memory impairment without inhibiting the initial inflammatory cascade. *Front Pharmacol* 2021; 11: 603979.

105. de Las Casas-Engel M and Corbi AL. Serotonin modulation of macrophage polarization: inflammation and beyond. *Adv Exp Med Biol* 2014; 824: 89–115.

106. Chen F, Danladi J, Ardalan M, et al. The rat hippocampal gliovascular system following one week vortioxetine and fluoxetine. *Eur Neuropsychopharmacol* 2021; 42: 45–56.

107. Fiebich B, Akundi R, Lieb K, et al. Antiinflammatory effects of 5-HT3 receptor antagonists in lipopolysaccharide-stimulated primary human monocytes. *Scand J Rheumatol Suppl* 2004; 33: 28–32.

108. Stratz C, Bhatia HS, Akundi RS, et al. The anti-inflammatory effects of the 5-HT3 receptor antagonist tropisetron are mediated by the inhibition of p38 MAPK activation in primary human monocytes. *Int Immunopharmacol* 2012; 13: 398–402.

109. Kim JJ, Bridle BW, Ghia JE, et al. Targeted inhibition of serotonin type 7 (5-HT7) receptor function modulates immune responses and reduces the severity of intestinal inflammation. *J Immunol* 2013; 190: 4795–4804.

110. Gupta D, Prabhakar V and Radhakrishnan M. 5HT3 receptors: target for new antidepressant drugs. *Neurosci Biobehav Rev* 2016; 64: 311–325.

111. Adamo D, Pecoraro G, Coppola N, et al. Vortioxetine versus other antidepressants in the treatment of burning mouth syndrome: an open-label randomized trial. *Oral Dis* 2021; 27: 1022.

112. Chen G, Hojer AM, Areberg J, et al. Vortioxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2018; 57: 673–686.

113. Guan S, Zou Y, Jia B, et al. Pharmacokinetic and metabolic studies of vortioxetine in rats using ultra high performance liquid chromatography with tandem mass spectrometry. *J Sep Sci* 2018; 41: 4469–4479.

114. Dale E, Grunnet M, Pehrson AL, et al. The multimodal antidepressant vortioxetine may facilitate pyramidal cell firing by inhibition of 5-HT3 receptor expressing interneurons: an in vitro study in rat hippocampus slices. *Brain Res* 2018; 1689: 1–11.

115. Miao J, Wang G, Hou J, et al. Pharmacokinetics and safety of vortioxetine in Chinese population. *Adv Ther* 2019; 36: 3134–3146.

116. Findling RL, Robb AS, DelBello M, et al. Pharmacokinetics and safety of vortioxetine in pediatric patients. *J Child Adolesc Psychopharmacol* 2017; 27: 526–534.

117. Vieta E, Florea I, Schmidt SN, et al. Intravenous vortioxetine to accelerate onset of effect in major depressive disorder: a 2-week, randomized, double-blind, placebo-controlled study. *Int Clin Psychopharmacol* 2019; 34: 153–160.

118. Areberg J, Søgaard B and Hojer AM. The clinical pharmacokinetics of Lu AA21004 and its major metabolite in healthy young volunteers. *Basic Clin Pharmacol Toxicol* 2012; 111: 198–205.
119. Hvenegaard MG, Bang-Andersen B, Pedersen H, et al. Identification of the cytochrome P450 and other enzymes involved in the in vitro oxidative metabolism of a novel antidepressant, Lu AA21004. Drug Metab Dispos 2012; 40: 1357–1365.

120. Spina E and Santoro V. Drug interactions with vortioxetine, a new multimodal antidepressant. Riv Psichiatr 2015; 50: 210–215.

121. Chen C and Shan W. Pharmacological and non-pharmacological treatments for major depressive disorder in adults: a systematic review and network meta-analysis. Psychiatry Res 2019; 281: 112595.

122. Chen G, Zhang W and Serenko M. Lack of effect of multiple doses of vortioxetine on the pharmacokinetics and pharmacodynamics of aspirin and warfarin. J Clin Pharmacol 2015; 55: 671–679.

123. McIntyre RS. The role of new antidepressants in clinical practice in Canada: a brief review of vortioxetine, levomilnacipran ER, and vilazodone. Neuropsychiatr Dis Treat 2017; 13: 2913–2919.

124. de Bartolomeis A, Fagiolini A and Maina G. Identification of the cytochrome P450 system. Psychiatry Clin Neurosci 2018; 72: 64–72.

125. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant: what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014; 68: 60–82.

126. Chokka PR and Hankey JR. Assessment and management of sexual dysfunction in the context of depression. Ther Adv Psychopharmacol 2018; 8: 13–23.

127. Jacobsen P, Zhong W, Nomikos G, et al. Paroxetine, but not vortioxetine, impairs sexual functioning compared with placebo in healthy adults: a randomized, controlled trial. J Sex Med 2019; 16: 1638–1649.

128. Jacobsen PL, Nomikos GG, Zhong W, et al. Clinical implications of directly switching antidepressants in well-treated depressed patients with treatment-emergent sexual dysfunction: a comparison between vortioxetine and escitalopram. CNS Spectr 2020; 25: 50–63.

129. Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol 2016; 30: 242–252.

130. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391: 1357–1366.

131. Nissen TD, Laursen B, Viardot G, et al. Effects of vortioxetine and escitalopram on electroencephalographic recordings: a randomized, crossover trial in healthy males. Neuroscience 2020; 424: 172–181.

132. Wang G, Geslum M, Filippov G, et al. Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. Curr Med Res Opin 2015; 31: 785–794.

133. Nishimura A, Aritomi Y, Sasai K, et al. Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. Psychiatry Clin Neurosci 2018; 72: 64–72.

134. Thase ME, Mahableshwarkar AR, Dragheim M, et al. A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. Eur Neuropsychopharmacol 2016; 26: 979–993.

135. Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. J Clin Psychiatry 2015; 76: 583–591.

136. Jacobsen PL, Mahableshwarkar AR, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. J Clin Psychiatry 2015; 76: 575–582.

137. Mahableshwarkar AR, Jacobsen PL and Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Curr Med Res Opin 2013; 29: 217–226.

138. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry 2012; 73: 953–959.

139. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled,
active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol* 2012; 15: 589–600.

140. Baldwin DS, Hansen T and Florea I. Vortioxetine (Lu AA21004) in the long-term open-label treatment of major depressive disorder. *Curr Med Res Opin* 2012; 28: 1717–1724.

141. Montgomery SA, Nielsen RZ, Poulsen LH, et al. A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. *Hum Psychopharmacol* 2014; 29: 470–482.

142. Boulenger JP, Loft H and Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol* 2012; 27: 215–223.

143. Katona C, Hansen T and Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 2014; 29: 138–149.

144. Alam MY, Jacobsen PL, Chen Y, et al. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible-dose, 52-week extension study. *Int Clin Psychopharmacol* 2014; 29: 36–44.

145. Vieta E, Loft H and Florea I. Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder. *Eur Neuropsychopharmacol* 2017; 27: 877–884.

146. Thase ME, Danchenko N, Brignone M, et al. Comparative evaluation of vortioxetine as a switch therapy in patients with major depressive disorder. *Eur Neuropsychopharmacol* 2017; 27: 773–781.

147. Papakostas GI, Nielsen RZ, Dragheim M, et al. Efficacy and tolerability of vortioxetine versus agomelatine, categorized by previous treatment, in patients with major depressive disorder switched after an inadequate response. *J Psychiatr Res* 2018; 101: 72–79.

148. Llorca PM, Lançon C, Brignone M, et al. Relative efficacy and tolerability of vortioxetine versus selected antidepressants by indirect comparisons of similar clinical studies. *Curr Med Res Opin* 2014; 30: 2589–2606.

149. Wagner G, Schultes MT, Titscher V, et al. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. *J Affect Disord* 2018; 228: 1–12.

150. Meeker AS, Herink MC, Haxby DG, et al. The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: a systematic review and meta-analysis. *Syst Rev* 2015; 4: 21. Published 2015 Mar 1.

151. Sobieraj DM, Martinez BK, Hernandez AV, et al. Adverse effects of pharmacologic treatments of major depression in older adults. *J Am Geriatr Soc* 2019; 67: 1571–1581.

152. Li G, Wang X and Ma D. Vortioxetine versus duloxetine in the treatment of patients with major depressive disorder: a meta-analysis of randomized controlled trials. *Clin Drug Investig* 2016; 36: 509–517.

153. Christensen MC and Munro V. Cost per successfully treated patient for vortioxetine versus duloxetine in adults with major depressive disorder: an analysis of the complete symptoms of depression and functional outcome. *Curr Med Res Opin* 2018; 34: 593–600.

154. Florea I, Danchenko N, Brignone M, et al. The effect of vortioxetine on health-related quality of life in patients with major depressive disorder. *Clin Ther* 2015; 37: 2309–2323.e6.

155. Pae CU, Wang SM, Han C, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. *J Psychiatr Res* 2015; 64: 88–98.

156. Baldwin DS, Florea I, Jacobsen PL, et al. A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. *J Affect Disord* 2016; 206: 140–150.

157. Kong W, Deng H, Wan J, et al. Comparative remission rates and tolerability of drugs for generalised anxiety disorder: a systematic review and network meta-analysis of double-blind randomized controlled trials. *Front Pharmacol* 2020; 11: 580858.

158. Shah A and Northcutt J. An open-label, flexible dose adaptive study evaluating the efficacy of vortioxetine in subjects with panic disorder. *Ann Gen Psychiatry* 2018; 17: 19.

159. Perna G, Aliciati A, Riva A, et al. Long-term pharmacological treatments of anxiety disorders: an updated systematic review. *Curr Psychiatry Rep* 2016; 18: 23.
160. Liebowitz MR, Careri J, Blatt K, et al. Vortioxetine versus placebo in major depressive disorder comorbid with social anxiety disorder. *Depress Anxiety* 2017; 34: 1164–1172.

161. McIntyre RS, Xiao HX, Syeda K, et al. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. *CNS Drugs* 2015; 29: 577–589.

162. Baune BT, Sluth LB and Olsen CK. The effects of vortioxetine on cognitive performance in working patients with major depressive disorder: a short-term, randomized, double-blind, exploratory study. *J Affect Disord* 2018; 229: 421–428.

163. Subramaniapillai M, Mansur RB, Zuckerman H, et al. Association between cognitive function and performance on effort based decision making in patients with major depressive disorder treated with vortioxetine. *Compr Psychiatry* 2019; 94: 152113.

164. Lenze EJ, Stevens A, Waring JD, et al. Augmenting computerized cognitive training with vortioxetine for age-related cognitive decline: a randomized controlled trial. *Am J Psychiatr* 2020; 177: 548–555.

165. Blumberg MJ, Vaccarino SR and McInerney SJ. Procognitive effects of antidepressants and other therapeutic agents in major depressive disorder. *J Clin Psychiatry* 2020; 81: 19r13200. Published 2020 Jul 21.

166. Cao B, Park C, Rosenblat JD, et al. Changes in sleep predict changes in depressive symptoms in depressed subjects receiving vortioxetine: an open-label clinical trial. *J Psychopharmacol* 2019; 33: 1388–1394.

167. Liguori C, Ferini-Strambi L, Izzì F, et al. Preliminary evidence that vortioxetine may improve sleep quality in depressed patients with insomnia: a retrospective questionnaire analysis. *Br J Clin Pharmacol* 2019; 85: 240–244.

168. Adamo D, Pecoraro G, Aria M, et al. Vortioxetine in the treatment of mood disorders associated with burning mouth syndrome: results of an open-label, flexible-dose pilot study. *Pain Med* 2019; 21: 185–194.

169. Wilson S, Højer AM, Buchberg J, et al. Differentiated effects of the multimodal antidepressant vortioxetine on sleep architecture: part 1, a pharmacokinetic/pharmacodynamic comparison with paroxetine in healthy men. *J Psychopharmacol* 2015; 29: 1085–1091.

170. Matsuno K, Nakamura K, Aritomi Y, et al. Pharmacokinetics, safety, and tolerability of vortioxetine following single- and multiple-dose administration in healthy Japanese adults. *Clin Pharmacol Drug Dev* 2018; 7: 319–331.

171. Sutherland AM, Nicholls J, Bao J, et al. Overlaps in pharmacology for the treatment of chronic pain and mental health disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 87: 290–297.

172. Buckman JEJ, Underwood A, Clarke K, et al. Risk factors for relapse and recurrence of depression in adults and how they operate: a four-phase systematic review and meta-synthesis. *Clin Psychol Rev* 2018; 64: 13–38.