

Graylands Hospital Drug Bulletin Vortioxetine

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The release of new drugs in psychiatry has slowed in recent years and most of the latest released new drugs have been minor changes on the theme of existing medications with the exception of agomelatine and vortioxetine. These two medications have promised novel mechanisms of action.

Vortioxetine (Lu AA21004) was Therapeutic Goods Administration (TGA) registered on 31 March 2014 for the treatment of major depressive disorder (MDD) in adults including prevention of relapse. Regulatory approval of vortioxetine was granted in the USA and Europe during 2013.

Mechanism of Action

Vortioxetine has been reported to selectively inhibit reuptake of serotonin (5-HT) via the serotonin transporter¹ (SERT), to be an antagonist at 5-HT_{1D}, 5-HT₃ and 5-HT₇ receptors, a partial agonist at 5-HT_{1B} receptors and a full agonist at 5-HT_{1A} receptors.^{2,3} The relative contributions of the various neurochemical effects of vortioxetine are not well understood but cause modulation of brain serotonergic, dopaminergic, histaminic, cholinergic, gamma-aminobutyric acid-ergic and glutaminergic systems. Hence, vortioxetine has been described as a 'multimodal' antidepressant.⁴

In animal studies vortioxetine has been shown to differ from Selective Serotonin Reuptake Inhibitors (SSRIs) in promoting several measures of synaptic transmission, neuroplasticity and dendritic branching to a larger degree than SSRIs.² Based on clinical efficacy studies, vortioxetine may exert antidepressant effects at SERT occupancy as low as 50% unlike SSRIs and Serotonin and Noradrenalin Reuptake Inhibitors (SNRIs) which require 80%.²

Pharmacokinetics

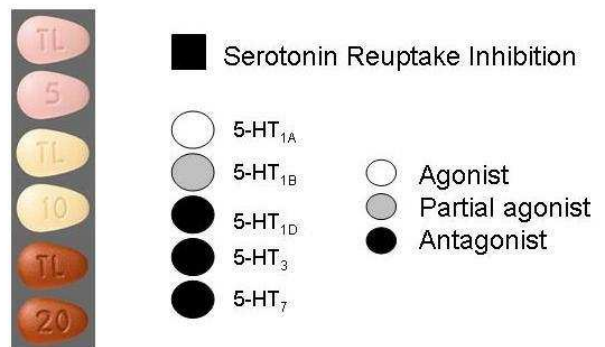
Following multiple oral doses, maximum plasma concentrations are reached after 7–8 hours.^{2,5} Bioavailability is 75% and vortioxetine's mean terminal half-life is about 66 hours.⁵ Steady state

is reached in about 2 weeks. It is highly protein bound (>99%).²

Vortioxetine is mainly metabolised by cytochrome P450 (CYP) 2D6 and metabolites are eliminated in the faeces (59%) and urine (26%).⁵ No metabolites are considered likely to contribute to its therapeutic activity and it shows no significant inhibition or induction of CYP enzymes^{2,6} or significant effects on p-glycoprotein.⁷

Dose reduction should be considered if co-administration of strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine) is necessary. Conversely, the vortioxetine dose may need to be increased if strong CYP2D6 inducers (e.g. rifampicin, carbamazepine) are used. CYP2D6-inferred metabolic status was shown to have a significant impact on clearance, where extensive metabolisers in general had 1.9 times the clearance of poor metabolisers.⁵

Vortioxetine



Side Effects

Clinical studies suggest that nausea was the most frequent adverse event and its frequency appears to be dose-related.⁷ The incidence of mild nausea ranged from 14% to 20% in patients taking vortioxetine in doses of 5, 10, 15, or 20 mg/d; rates of moderate nausea were from 7% to 13%. The incidence of severe nausea was below 2% in all groups.^{4,8} However, pooled discontinuation rates due to adverse events were low over an extended period suggesting

that nausea is unlikely to interfere with compliance during acute treatment and maintenance therapy.⁸

The incidence of sexual dysfunction varies from study to study. It is thought that the incidence of sexual dysfunction is significantly higher than placebo but less than duloxetine. Vortioxetine appears to cause sexual dysfunction in a dose-dependent manner.⁴ It is thought that the lower level of sexual dysfunction compared to SSRIs is due to the lower occupancy of SERT.²

Like other serotonin antidepressants, vortioxetine can cause increased bleeding tendency.⁴ Hyponatremia can occur and electrolytes should be checked 6 weeks after starting vortioxetine.⁴

The incidence of several other adverse events commonly associated with antidepressant treatment, such as insomnia, fatigue, sedation, and somnolence, was low.^{4,8} Vortioxetine had no significant effect on body weight in the dose ranges tested so far.⁴ Headache does not appear to be a problem in contrast to other serotonergic drugs.

Cardiac Effects

Short-term trials have showed that vortioxetine treatment does not lead to any clinically significant changes in blood pressure and heart rate and does not appear to significantly increase QTc interval duration.⁷

Dosage

The recommended starting dose is 10mg daily except in patients who are older than 65 or are known slow CYP2D6 metabolisers who should start on 5mg daily.⁴ Depending on response, the dose can be reduced or increased to 20mg, bearing in mind vortioxetine takes 2 weeks to reach steady state. Studies have shown that a dose of 5-20mg daily corresponds to SERT occupancy of 50 to 80%.² Vortioxetine is taken once daily without regard to meals.

A large number of placebo-controlled randomised controlled trials have been performed evaluating the efficacy of vortioxetine, probably because of an unanticipated regional difference in its dose-response performance.⁹ The 5mg dose was found to be more effective than placebo throughout most of the world except in 2 studies conducted in the United States. A second wave of studies was then

undertaken to determine if higher doses (15-20mg) were effective in the United States. It has been noted that “the observed differences in efficacy almost certainly pertain to problems with signal detection in contemporary RCTs of antidepressants, which, in the case of the studies of vortioxetine, was more evident in the United States than elsewhere in the world.”⁶

Special Populations

Elderly Patients

The recommended starting dose is 5 mg daily. In elderly healthy subjects (aged ≥65 years), the exposure to vortioxetine increased up to 27% (C_{max} and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10 mg/day.

Renal impairment

No dose adjustment is needed.

Following a single dose of 10 mg vortioxetine, renal impairment (mild, moderate, or severe) caused modest exposure increases (up to 11%), compared to healthy matched controls. In patients with end-stage renal disease, only a small fraction of vortioxetine was lost during the dialysis process (AUC and C_{max} were 13% and 27% lower) following a single 10 mg dose of vortioxetine.

Hepatic impairment

No dose adjustment is needed.

Following a single dose of 10 mg vortioxetine, no impact of mild or moderate hepatic impairment (Child-Pugh Criteria A or B) was observed on the pharmacokinetics of vortioxetine (changes in AUC less than 10%).

CYP2D6 poor metabolisers

No dose adjustment is needed.

The plasma concentration of vortioxetine was approximately two times higher in CYP2D6 poor metabolisers than in extensive metabolisers.

Gender and Race

No dose adjustment is needed.

Systemic exposures are similar between males and females of comparable body size and race or ethnicity had no apparent effect on the pharmacokinetics of vortioxetine

Interactions

Vortioxetine and its metabolites showed, at most, weak inhibition or induction of CYP isozymes. These levels of effect on CYP enzymes are unlikely to be of clinical significance.



The potential for pharmacokinetic drug interactions mediated by vortioxetine acting as a substrate or inhibitor of human P-glycoprotein was investigated and no significant effects were found.

Because of the risk of serotonin syndrome, concomitant use of monoamine oxidase inhibitors (MAOIs) is contraindicated during vortioxetine treatment and for 14 days after it is stopped. Serotonin toxicity can also occur with other serotonergic medicines such as sumatriptan, tramadol and St John's wort. Prescribers should be vigilant for symptoms if these drugs are taken concurrently.¹

Pregnancy

Vortioxetine is a pregnancy category B3 drug. Although there is no human data, animal studies found that vortioxetine reduced foetal weight and delayed ossification. In rats, survival of pups was lower in mothers receiving vortioxetine.¹⁰

Place in Therapy

While vortioxetine is classified as a "multimodal" antidepressant by some, the US Federal Drug Administration (FDA) still classifies it as an SSRI. The FDA did not conclude that the effects at the various receptors have clinically significant benefit.^{6,9} Some reviews conclude that the evidence gathered so far does not show that vortioxetine has any clear advantage over other currently available treatment options.⁴ This is in direct contrast to opinions expressed by other authors who say that vortioxetine is the first antidepressant that has demonstrated replicated evidence of efficacy in mitigating cognitive dysfunction across the adult age range in MDD.⁷

It has been reported that many patients, including those considered to be good responders to antidepressants, continue to suffer from residual, subsyndromal, symptomatology as well as presenting with persistent functional impairment e.g. sleepiness, fatigue and executive dysfunction^{11,12} Vortioxetine has been shown to significantly improve objective and subjective measures of cognition. The effects were largely independent on its effects on improving depressive symptoms.^{11,13} The multimodal mechanism of vortioxetine may be involved in the procognitive activity and low incidence of sexual side effects.¹²

Clinicians may wish to change to vortioxetine when

1. the patient complains about cognitive function impairment after depression has been improved
2. treatment related decline in sexual function

3. patients show inadequate therapeutic response.¹²

Cost, Pharmaceutical Benefits Scheme Application and Formulary

The Pharmaceutical Benefits Advisory Committee (PBAC) rejected the submission on the basis that the clinical place of vortioxetine relative to SSRIs and (SNRIs) was not made clear in the evidence submitted and on the basis that the PBAC did not accept the claim of non-inferiority of vortioxetine compared to duloxetine.¹⁴

The PBAC response was that the evidence presented by Lundbeck did not demonstrate sufficient benefit for vortioxetine to be listed.¹⁴ At the time of writing, vortioxetine remains non-formulary in NMAHS.

Until vortioxetine is listed on the PBS, the dispensed price will be around \$70 per month regardless of strength.

Serotonin Receptor Effects of Vortioxetine

While the exact mechanism of action of vortioxetine remains unclear, it is worth considering the theories of the interplay of different serotonin receptors to better understand vortioxetine's effects. Serotonin neurons often lack direct synaptic contacts, and in many cases 5HT receptors have been detected on neurons that do not receive serotonergic innervation. This suggests that certain areas of the brain, 5HT is released diffusely by volume transmission and acts more as a neuromodulator whose function might be to maintain homeostasis in the brain.¹⁵

The serotonin receptor subtype 5HT_{1A} is present as both somatodendritic presynaptic autoreceptors and as postsynaptic receptors. Presynaptic 5HT_{1A} autoreceptors act as a negative feedback mechanism which reduces the effects of antidepressant drugs. The effectiveness of this negative feedback pathway in inhibiting the effects of SSRIs declines with prolonged treatment. It is thought that this feedback loop probably explains much of the slow and delayed clinical action of anti-depressant drugs¹⁶ in that before SERT inhibition shows antidepressant effect, these receptors must be desensitised. Vortioxetine stimulates 5HT_{1A} presynaptic autoreceptors on the serotonin cell body and dendrites as well as blocks SERT. This is believed to hasten the desensitisation of 5HT_{1A} presynaptic receptors.

The stimulation of postsynaptic 5-HT_{1A} receptors is beneficial for the antidepressant action having anxiolytic and antidepressant effects. 5HT_{1A} receptors also act as an accelerator for downstream dopamine release.¹⁷

5HT_{1B} presynaptic receptors also inhibit further serotonin release while 5HT₇ receptors indirectly inhibit serotonin release via GABA neurons. The full or partial antagonism of these receptors by vortioxetine interferes with their negative feedback function and disinhibits serotonin release. The continuing presence of MAO activity ensures serotonin levels do not rise to dangerous levels.¹⁸ Postsynaptic 5HT_{1B} receptors are also known as heteroreceptors and when stimulated have an antidepressant effect¹⁶

Vortioxetine is a full agonist at 5HT_{1A}, a partial agonist at 5HT_{1B} and a full antagonist at 5HT_{1D} and 5HT₇. The net effect is to rapidly downregulate one negative feedback pathway and to directly reduce other inhibitory pathways.

Serotonin stimulation of 5HT₃ causes increased GABA release from GABAergic interneurons which in turn inhibits cortical pyramidal neurons which then prevents amplification of serotonin release by downstream glutamate.¹⁹ Serotonin regulates the downstream release of other neurotransmitters including noradrenaline (NA) and acetylcholine (ACh). Because vortioxetine increases serotonin release and also blocks 5HT₃, both NA and ACh release are disinhibited. Enhanced release of NA and ACh are thought to have both antidepressant and procognitive effects.¹⁹

Yet another negative feed-back upon serotonin release is 5HT₇ receptors on GABA neurons in the raphe. When serotonin stimulates these receptors, inhibitory GABA is released, which shuts off further serotonin release. Vortioxetine is an antagonist at 5HT₇ and blocks this inhibitory pathway.

Conclusion

There is much evidence demonstrating the multimodal action of vortioxetine. If it is proven to offer advantages over existing antidepressants in the general population, then vortioxetine will be a major step forward in the treatment of depression. It is worrying that the FDA dismissed the unusual receptor activity as irrelevant and classified vortioxetine as an SSRI.

Until vortioxetine is accepted as significantly different to other antidepressants, it will remain as a second line treatment for patients who have shown inadequate therapeutic response and possible for patients suffering from antidepressant induced sexual dysfunction.

Vortioxetine at a glance

Brand: Brintellix

Form: Tablets

Strengths: 5mg, 10mg, 15mg, 20mg

Indication: Treatment of Major Depressive Disorder

Usual Starting Dose: 10mg daily

Starting Dose in Elderly: 5mg

Maximum recommended dose: 20mg

Can be taken with or without food, swallowed whole, once a day, either in the morning or evening

Time to Steady State: 14 days

Most Common Side Effect:

Short term nausea

Other Common Side Effects:

diarrhoea, dizziness, constipation and vomiting.

Sexual Dysfunction: dose related

Weight Gain: Not associated

QTc Prolongation: Not Associated

Interactions:

Contraindicated with MAOIs

Not recommended with other serotonergic drugs

May be affected by drugs which strongly affect CYP2D6

Pregnancy: Category B3. It is expected that vortioxetine will pass into breast milk

Treatment Discontinuation: can be abruptly stopped

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