

Drug interactions with vortioxetine, a new multimodal antidepressant

Interazioni farmacologiche della vortioxetina, un nuovo antidepressivo ad azione multimodale

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SUMMARY. This article summarized the available knowledge on clinically relevant drug interactions of vortioxetine, a new antidepressant with a “multimodal” serotonergic mechanism of action, recently approved for the treatment of major depressive disorder. Although information is still limited and mainly based on studies performed in healthy volunteers, vortioxetine appears to have a favorable drug interaction profile. Concerning the potential for pharmacokinetic drug interactions, vortioxetine has little to no effect on various cytochrome P450 (CYP) isoforms and therefore is not expected to markedly affect plasma concentrations of other medications metabolized by these enzymes. This is a major advantage when compared to other antidepressants which are known to inhibit the activity of one or more CYP isoforms. On the other hand, dosage adjustments may be required when vortioxetine is coadministered with strong CYP2D6 inhibitors or broad-spectrum CYP inducers. Vortioxetine carries a relatively low risk for pharmacodynamic drug interactions, at least as compared to first-generation antidepressants. Like other antidepressants enhancing serotonergic activity, vortioxetine is associated with a potential risk of serotonin syndrome when used in combination with other serotonergic agents. Based on all available clinical data, vortioxetine has no increased risk of serotonin syndrome when used without other serotonergic agents and at therapeutic doses.

KEY WORDS. vortioxetine, drug interactions, pharmacokinetics, pharmacodynamics, cytochrome P450.

RIASSUNTO. In questo articolo vengono riassunte le attuali conoscenze sulle interazioni farmacologiche clinicamente rilevanti della vortioxetina, un nuovo farmaco antidepressivo con un meccanismo d'azione multimodale sul sistema serotonergico, recentemente approvato per il trattamento del disturbo depressivo maggiore. Sebbene i dati disponibili siano ancora limitati e basati prevalentemente su studi condotti su volontari sani, la vortioxetina sembra presentare un favorevole profilo di interazioni farmacologiche. Per quel che riguarda il potenziale di interazioni farmacocinetiche, la vortioxetina non interferisce con l'attività degli enzimi del citocromo P450 e conseguentemente non dovrebbe modificare le concentrazioni plasmatiche di farmaci metabolizzati a opera di questi enzimi. Questo costituisce un importante vantaggio rispetto ad altri farmaci antidepressivi che inibiscono l'attività di uno più isoenzimi del citocromo P450. Un aggiustamento dello schema di dosaggio potrebbe invece rendersi necessario quando la vortioxetina è somministrata insieme a potenti inibitori del CYP2D6 o a induttori enzimatici ad ampio spettro. La vortioxetina sembra mostrare un più basso rischio di interazioni farmacodinamiche rispetto agli antidepressivi di prima generazione. Tuttavia, come per altri farmaci antidepressivi, un trattamento con vortioxetina potrebbe dar luogo a una sindrome serotonergica in caso di contemporanea somministrazione con altri farmaci che potenziano la trasmissione serotonergica. I dati clinici disponibili, invece, non mostrano un rischio di sindrome serotonergica quando la vortioxetina viene somministrata alle dosi terapeutiche e senza concomitanti altri farmaci ad azione serotonergica.

PAROLE CHIAVE. vortioxetina, interazioni farmacologiche, farmacocinetica, farmacodinamica, citocromo P450.

INTRODUCTION

Multiple drug therapy is common in clinical psychiatry practice and carries the risk of drug interactions. A drug interaction occurs when the effectiveness or toxicity of a drug is altered by the concomitant administration of another pharmacological agent. In a few cases drug interactions may prove beneficial, leading to increased efficacy or reduced risk of unwanted effects, and therefore certain drug combinations may be used advantageously in clinical practice. However, more often, drug interactions are of concern because the outcome of concurrent drug administration is diminished therapeutic efficacy or increased toxicity of one or more of the administered compounds.

The potential for drug interactions represents an important issue in the evaluation of many psychotropic drugs including antidepressants. Antidepressant medications may be involved in drug interactions as they are commonly prescribed in combination with other drugs used to treat concomitant psychiatric, neurological or somatic disorders or to augment antidepressant response in refractory depression¹. Currently available antidepressants differ considerably in their potential for pharmacological interactions. Certain first-generation antidepressants, namely monoamine oxidase inhibitors (MAOIs), have been associated with a significant risk of potentially harmful pharmacodynamic drug interactions which has contributed to a gradual decline in their uti-

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lization in clinical practice². In addition, tricyclic antidepressants (TCAs) have a relatively high potential for pharmacodynamic interactions as they bind to multiple receptors types (muscarinic cholinergic, α_1 -adrenergic, H_1 -histaminergic receptors)². Newer antidepressants including a number of selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), may cause clinically relevant pharmacokinetic interactions with other medications through their ability to inhibit one or more cytochrome P450 (CYP) enzymes¹⁻⁷. Although the prevalence of clinically relevant drug interactions with antidepressants appears to be rather low and adverse drug interactions are often predictable, the use of antidepressants with a low potential for drug interactions is desirable, especially in elderly patients, who may take many medications simultaneously⁷.

Vortioxetine is a new 'multimodal' antidepressant with a complex mechanism of action, which includes inhibition of the serotonin (5-HT) transporter protein and strong affinity for several serotonergic receptors⁸. It is approved in the US and the EU for the treatment of adults with major depressive disorder⁹. In recent years, a number of comprehensive reviews have been published describing the basic and clinical pharmacology of vortioxetine, and its efficacy and tolerability in the treatment of major depressive disorder⁹⁻¹¹.

Aim of the present article was to review the drug interaction potential of vortioxetine. Available drug interaction studies have been summarized and the drug interaction profile of vortioxetine has been compared with that of other antidepressants.

PHARMACOLOGICAL PROFILE OF VORTIOXETINE

Knowledge of the basic pharmacological properties of vortioxetine is essential to understand and predict its potential for drug interactions.

Pharmacokinetics

The pharmacokinetics of vortioxetine are linear and dose-proportional following once daily administration of 2.5 to 60 mg doses¹²⁻¹⁴. Vortioxetine is absorbed slowly, but almost completely, after oral administration and the post-dose peak plasma concentration (C_{max}) is reached within 7 to 11 hours (T_{max}). The absolute bioavailability of vortioxetine is 75%. Food has no effect on the pharmacokinetics of vortioxetine. Vortioxetine is extensively distributed into the extravascular compartment and has a large volume of distribution (approximately 2,600 L). The plasma protein binding is 98%, and is independent of plasma concentration.

Vortioxetine is extensively metabolized in the liver, primarily via oxidation and subsequent conjugation with glucuronic acid. *In vitro* studies using human liver microsomes and recombinant enzymes have indicated that several CYP isoenzymes are involved in the oxidative biotransformation of vortioxetine, including CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6¹⁵. Vortioxetine is metabolized to its major carboxylic acid metabolite, Lu-AA34443 (pharmacologically inactive), mainly via the CYP2D6 pathway and poor metabolizers of CYP2D6 achieve twice the plasma concentrations of extensive metabolizers. A minor hydroxyl metabolite, Lu-AA39835, shows

similar 5-HT transporter inhibition to the parent compound but is not expected to penetrate the blood-brain barrier¹⁶. The mean elimination half-life is 66 hours and the mean oral clearance is 33 L/h. Approximately 2/3 of the inactive vortioxetine metabolites are excreted in the urine and approximately 1/3 in the feces. Only negligible amounts of vortioxetine are excreted in the feces. The steady-state plasma concentrations are typically attained within 2 weeks of dosing.

The pharmacokinetics of vortioxetine are not affected in a clinically meaningful way by sex, race, renal impairment (mild, moderate, severe or end-stage renal disease) or mild or moderate hepatic impairment¹³⁻¹⁴. Vortioxetine has not been studied in patients with severe hepatic impairment and caution should be exercised when treating these patients. The exposure to vortioxetine increased by up to 27% (C_{max} and AUC) in elderly healthy volunteers (aged ≥ 65 years) as compared to young healthy control subjects (aged ≤ 45 years) receiving multiple doses of 10 mg/day.

Pharmacodynamics

As with all currently available antidepressant agents, the mechanisms underlying the beneficial effects of vortioxetine are not fully understood. Vortioxetine has a very broad range of pharmacological properties and has been described as a "multimodal" antidepressant. In particular, vortioxetine is a 5-HT transporter inhibitor, 5-HT₃, 5-HT₇ and 5-HT_{1D} receptor antagonist, 5-HT_{1A} receptor agonist 5-HT_{1B} receptor partial agonist^{10,17}.

Vortioxetine binds to human 5-HT transporter with high affinity ($K_i = 1.6$ nM) and potently and selectively inhibits serotonin reuptake ($IC_{50} = 5.4$ nM) (18). This pharmacological action may represent the principal mechanism responsible for its antidepressant effect. Vortioxetine has a much lower affinity to the human noradrenaline ($K_i = 113$ nM) and dopamine ($K_i = 1,000$ nM) transporters¹⁸. It binds as an agonist to the human 5-HT_{1A} receptor with a K_i of 15 nM, as a partial agonist to the human 5-HT_{1B} receptor with a K_i of 33 nM, and as an antagonist to the human 5-HT₃, 5-HT₇ and 5-HT_{1D} receptors with K_i of 3.7, 19 and 54 nM, respectively¹⁸.

The net effect of this pharmacological profile is that vortioxetine increases levels of 5-HT, noradrenaline, dopamine, acetylcholine, histamine and glutamate in specific areas of the rat brain such as the ventral hippocampus and the medial prefrontal cortex, both known to be important in the neurobiology of depression and response to antidepressant treatment¹⁰. This activity across several systems may be responsible for the antidepressant- and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed in animal studies¹⁹. This broad pharmacological profile may provide the rationale for efficacy of vortioxetine in treating patients with major depressive disorder, including cognitive dysfunction and generalized anxiety disorder.

DRUG INTERACTIONS WITH VORTIOXETINE

Based on their mechanisms, drug interactions can be classified as either pharmacokinetic and pharmacodynamic¹. However, many interactions are multifactorial in nature and may involve a complex sequence of events both at pharma-

cokinetic and pharmacodynamic level. Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism or excretion of a drug and/or its metabolite(s) after the addition of pharmacological agent. These interactions are associated with a modification in plasma concentration of either the drug or its metabolite(s) and are easily identified by therapeutic drug monitoring. Pharmacodynamic interactions occur at the site of pharmacological action between drugs that have either similar or opposing mechanisms of action. These interactions are not usually associated with changes in plasma drug concentrations and, therefore, are less well recognized and documented.

Pharmacokinetic interactions

The majority of clinically relevant pharmacokinetic interactions with antidepressants arise as a consequence of drug-induced changes in hepatic metabolism, through inhibition or induction of CYP isoenzymes, and less frequently from changes in plasma protein binding¹. In recent years, however, the increasing recognition of the role played by drug transporters, notably P-glycoprotein, in the absorption, distribution and excretion of a wide variety of drugs including antidepressants has raised the possibility that other mechanisms may occasionally be involved¹. The potential for pharmacokinetic drug interactions is an important issue to consider during the development of new drugs. Since the risk of a drug interaction is an undesirable property of a drug, such an information should ideally be obtained already in the preclinical phase.

Effect of vortioxetine on the pharmacokinetics of other drugs

In vitro data have indicated that vortioxetine is not likely to inhibit or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or P-glycoprotein, suggesting a low potential to cause pharmacokinetic drug interactions with drugs metabolized by these enzymes¹⁶. While *in vitro* methodologies are extremely useful as screening tools to predict metabolic drug interactions, formal interaction studies in healthy volunteers and in patients are needed to confirm the magnitude of effect and to evaluate the clinical relevance^{20,21}.

In this respect, an exploratory *in vivo* cocktail study investigated the effect of multiple daily doses of vortioxetine 10 mg on the pharmacokinetics of probe substrates of CYP1A2 (caffeine), CYP2C9 (tolbutamide), CYP2D6 (dextromethorphan) and CYP3A4 (midazolam) in healthy subjects²². Vortioxetine co-administration did not affect pharmacokinetic parameters of caffeine, tolbutamide and midazolam, whereas it decreased plasma exposure of dextromethorphan by up to 24 %.

Subsequently, Chen et al.¹⁶ performed 3 clinical pharmacology studies in healthy volunteers to investigate the effect of vortioxetine on the pharmacokinetics of selected CYP substrates such as combined oral contraceptives (CYP3A substrates), bupropion (CYP2B6 substrate) and omeprazole (CYP2C19 substrate). In particular, these studies investigated the effect of multiple doses of vortioxetine, 10 mg daily, on the steady-state pharmacokinetics of combined oral contraceptives (ethinyl estradiol 30 mg/levonorgestrel 150 mg given once daily; n=28), on the steady-state pharmacokinetics of

bupropion (150 mg twice daily; n=60) and on the single-dose of omeprazole 40 mg (n=18). Steady-state concentrations of vortioxetine had no clinically meaningful effect on the steady-state pharmacokinetic parameters of ethinyl estradiol/levonorgestrel, bupropion or single-dose pharmacokinetics of omeprazole and its primary metabolite 5'-hydroxy-omeprazole.

Two separate randomized, placebo-controlled trials evaluated the effects of multiple doses of vortioxetine (10 mg/day) on the pharmacokinetics and pharmacodynamics of aspirin and warfarin in healthy volunteers²³. These studies were undertaken as other antidepressants that, like vortioxetine, interfere with serotonin reuptake inhibition (i.e., SSRIs and SNRIs) had been reported to potentially increase the risk of bleeding events, and concomitant administration with aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants was found to potentiate this risk^{7,24}. The blockade of serotonin uptake from circulation into platelets induced by SSRIs and SNRIs, leading to reduced platelet aggregation and prolonged bleeding time, may be the underlying biological mechanism for this adverse effect. These antidepressants may increase the risk of hemorrhage during warfarin treatment through two additional pharmacokinetic mechanisms: a) some SSRIs, particularly fluvoxamine and fluoxetine, may substantially increase the bleeding risk associated with warfarin through the inhibition of the CYP2C9-mediated oxidative metabolism of the more biologically active (S)-enantiomer of warfarin; b) certain SSRI and SNRIs with high protein binding (i.e., fluoxetine and duloxetine), when coadministered with another highly bound drug such as warfarin, may also increase the free plasma drug concentrations via displacement of protein bound drug, potentially increasing the risk of adverse events^{7,23}. In the aspirin study, 28 subjects received vortioxetine 10 mg or placebo once daily for 14 days, followed by coadministration with aspirin 150 mg once daily for 6 days, in 2 periods with a crossover design. In the warfarin study, 54 subjects were randomized after reaching target international normalized ratio (INR) values on warfarin to receive vortioxetine 10 mg or matching placebo once daily for 14 days, with all subjects receiving a maintenance dose of warfarin (1-10 mg). Coadministration with vortioxetine did not change the steady-state pharmacokinetic parameters of aspirin or its metabolite salicylic acid, and had no statistically significant effect on the inhibition of arachidonic acid-, adenosine-50-diphosphate-, or collagen-induced platelet aggregation at any time points. Coadministration of vortioxetine did not affect significantly the pharmacokinetics of (R)- and (S)-warfarin enantiomers, or the mean coagulation parameters of warfarin. As total warfarin (protein bound plus free drug) pharmacokinetics for both (R)- and (S)-warfarin, as well as INR and prothrombin values, did not change significantly with coadministration of these 2 drugs, it can be speculated that vortioxetine does not inhibit CYP2C9-mediated oxidative metabolism of (S)-warfarin and does not displace warfarin from plasma proteins. Moreover, vortioxetine was well tolerated when coadministered with aspirin or warfarin.

Overall, these studies conducted in healthy volunteers confirm the *in vitro* evidence that vortioxetine shows no significant induction or inhibition of CYP isozymes, suggesting a low propensity to markedly affect the pharmacokinetics of coadministered medications which are substrates of these

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enzymes¹⁶. Such a favourable CYP enzyme inhibitory profile represents a major advantage of vortioxetine in comparison with other newer antidepressants. With regard to this, a number of antidepressant agents are strong (i.e., fluoxetine and paroxetine) or moderate (i.e., duloxetine and bupropion) inhibitors of CYP2D6, while fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A4^{7,25} (Table 1). Potentially harmful drug interactions may occur when these antidepressants are co-administered with drugs metabolized by these isoforms, especially compounds with a narrow therapeutic index.

Effect of other drugs on the pharmacokinetics of vortioxetine

As earlier reported, many CYP isoforms (i.e., CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6) are involved in the oxidative metabolism of vortioxetine¹⁵. Theoretically, pharmacokinetic drug-drug interactions are expected when vortioxetine is combined with agents that inhibit or induce these enzymes. However, the potential for CYP inhibitors to markedly affect the pharmacokinetics of vortioxetine is relatively low because multiple CYP pathways are involved in its metabolism. On the other hand, the situation may be totally different for interactions involving enzyme induction as there is no limit to the inducing process.

Four formal pharmacokinetic studies were conducted in healthy subjects to evaluate the effect of inhibitors and inducers of the various CYP isoforms involved in the metabo-

lism of vortioxetine¹⁶. Study 1 explored the effect of multiple dosing of bupropion (CYP2D6 inhibitor) on the steady-state pharmacokinetics of vortioxetine (n=60); study 2 assessed the influence of a single dose of omeprazole (CYP2C19 inhibitor) on the steady-state pharmacokinetics of vortioxetine (n=18); study 3 examined the effect of multiple doses of the oral antifungals fluconazole (strong CYP2C19 inhibitor; moderate CYP2C9 and CYP3A4/5 inhibitor) and ketoconazole (strong CYP3A and P-gp inhibitor) on the single-dose pharmacokinetics of vortioxetine (n=36); study 4 evaluated the influence of rifampicin (broad CYP inducer) on the single-dose pharmacokinetics of vortioxetine (n=13). C_{max} and AUC and of vortioxetine increased when co-administered with bupropion (114 and 128%, respectively), fluconazole (15 and 46%, respectively) and ketoconazole (26 and 30%, respectively), and decreased by 51 and 72%, respectively, when vortioxetine was coadministered with rifampicin. On the other hand, no changes in C_{max} and AUC of vortioxetine were observed a single dose of omeprazole (CYP2C19 inhibitor) compared with vortioxetine alone. Concomitant administration of vortioxetine with CYP inhibitors and inducers was well tolerated with no marked increases in the frequency of adverse events, except with bupropion. When bupropion was added to vortioxetine monotherapy, the incidence of nausea, vomiting, insomnia and dizziness increased compared with when vortioxetine was administered alone. Nine of the 60 volunteers included in the bupropion study discontinued treatment due to adverse events such as nausea, dizziness, headache and diarrhea.

Table 1. Inhibitory effect of newer antidepressants on cytochrome P450 (CYP) enzymes

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	0	0	0	+	0
Escitalopram	0	0	0	0/+	0
Fluoxetine	+	++	+ / ++	+++	+ / +++
Fluvoxamine	+++	++	+++	+	++
Paroxetine	+	+	+	+++	+
Sertraline	0	+	0	+ / ++	+
Venlafaxine	0	0	0	+	+
Duloxetine	0	0	0	++	+
Mirtazapine	0	0	0	+	0
Reboxetine	0	0	0	+	+
Bupropion	0	0	0	++	0
Agomelatine	0	0	0	0/+	0
Vortioxetine	0	0	0	0	0

0= minimal or no inhibition; += mild inhibition; ++= moderate inhibition; +++= potent inhibition
 Modified from Spina and de Leon²⁵.

Based on these findings and depending on individual patient response, a dosage reduction may be considered when vortioxetine is co-administered with strong CYP2D6 inhibitors such as quinidine, fluoxetine, paroxetine and bupropion. Conversely, an increase in dosage should be considered if vortioxetine is to be co-administered with broad-spectrum CYP inducers such as rifampicin, carbamazepine, phenobarbital and phenytoin.

Pharmacodynamic interactions

Pharmacodynamic interactions take place at the site of drug action and are more difficult to identify and measure than pharmacokinetic interactions. These interactions can be additive (i.e., equal to the sum of the effects of the individual drugs), synergistic (i.e., the combined effects are greater than the expected from the sum of individual effects) or antagonistic (i.e., the combined effects are less than additive) and can be associated with beneficial effects or increased toxicity.

Vortioxetine has a “multimodal” serotonergic mechanism of action, involving reuptake inhibition and a range of effects on presynaptic and postsynaptic receptors. The use of vortioxetine, as common class effect, in combination with other serotonergic agents may theoretically lead to the serotonin syndrome, a potentially fatal adverse drug reaction, which may occur as a consequence of an excessive serotonergic agonism at both central and peripheral serotonin receptors^{26,27}. Medications that should be avoided because of the increased risk of serotonin syndrome when combined with vortioxetine include MAOIs, TCAs, SSRIs, SNRIs, buspirone, trazodone, triptans, Hypericum extracts, analgesics (e.g., tramadol, meperidine, fentanyl, oxycodone), drugs of abuse, and linezolid (an antibiotic used to treat gram-positive bacteria). According to the US prescribing information and the EU summary of product characteristics, the concomitant use of vortioxetine with irreversible non-selective MAOIs as well as reversible, selective (i.e., moclobemide) and non-selective (i.e., linezolid), MAOIs is contraindicated^{13,14}. Treatment with vortioxetine must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI and must be discontinued for at least 14 days before starting treatment with an irreversible non-selective MAOI.

As previously mentioned, case reports and observational studies have indicated that the use of drugs that inhibit serotonin reuptake may be associated with an increased risk of bleeding, in particular upper gastrointestinal bleeding^{7,24}. This risk may be increased even more if these drugs are used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Based on the pooled safety analysis across all clinical trials with vortioxetine, the bleeding risk associated with this antidepressant seems to be rather low²³. Moreover, the study by Chen et al.²³ documented that vortioxetine has no impact on the pharmacokinetics of aspirin or warfarin and does not affect coagulation parameters when coadministered with either drug. However, due to the small sample size and the use of healthy volunteers in these studies, large epidemiologic studies in depressed patients are required to fully confirm the lack of association between vortioxetine and the increased risk of bleeding when coadministered with NSAIDs and anticoagulants. Therefore, caution is advised when vortioxetine is given to patients taking anticoagulants and/or medicinal products known to affect platelet function^{13,14}.

CONCLUSIONS

Drug interactions have become an important but preventable iatrogenic complication. The issue of drug interactions with antidepressants is of great clinical concern if we consider that the number of prescriptions of these compounds is generally growing in the population, particularly in the elderly²⁸. The recommended duration of treatment tend to increase, thus elevating the likelihood of coprescription with other medications. Moreover, some newer antidepressants are also used to treat psychiatric disorders other than depression (e.g. anxiety disorders) and non-psychiatric conditions (e.g. neuropathic pain and fibromyalgia) and are increasingly prescribed among general practitioners^{29,30}. However, despite millions of exposures, the prevalence of clinically relevant drug interactions with antidepressants appears to be relatively low^{31,32}.

The present article summarized the available knowledge on clinically relevant drug interactions involving vortioxetine, a multimodal antidepressant recently introduced into clinical practice. Although information is still limited and mainly based on studies performed in healthy volunteers, vortioxetine appears to have a favorable drug interaction profile. Concerning the potential for pharmacokinetic drug interactions, vortioxetine has little to no effect on various CYP isoforms and therefore is not expected to significantly affect the pharmacokinetics of CYP substrates at the recommended dosages. This is a major advantage when compared to other antidepressants which are known to inhibit the activity of one or more CYP isoforms. Moreover, as multiple CYP enzymes contribute to the metabolism of vortioxetine, it is unlikely that CYP inhibitors may significantly affect its pharmacokinetics. On the other hand, dosage adjustments may be required when vortioxetine is coadministered with strong CYP2D6 inhibitors or broad-spectrum CYP inducers. Vortioxetine carries a relatively low risk for pharmacodynamic drug interactions, at least as compared to first-generation antidepressants. Like other antidepressants enhancing serotonergic activity, vortioxetine could be associated with an increased risk of serotonin syndrome when used in combination with other serotonergic agents. Based on all available clinical data, vortioxetine has no increased risk of serotonin syndrome when used without other serotonergic agents and at therapeutic doses.

Further studies in psychiatric patients are needed to better define the drug interaction profile of vortioxetine and to fully confirm this favourable preliminary evidence.

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BIBLIOGRAFIA

1. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clin Ther* 2008; 30: 1206-7.
2. Spina E, Perucca E. Newer and older antidepressants. A comparative review of drug interactions. *CNS Drugs* 1994; 2: 479-97.
3. Lane RM. Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. *Int Clin Psychopharmacol* 1996; 11 (suppl 5): 31-61.

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4. Hiemke C, Hartter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; 85: 11-28.
5. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; 3: 13-37.
6. Nemeroff CB, Preskorn S, Devane CL. Antidepressant drug-drug interactions: clinical relevance and risk management. *CNS Spectr* 2007; 12 (suppl 7): 1-13.
7. Spina E, Trifiro G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs* 2012; 26: 39-67.
8. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): enhancing serotonin release by combining serotonin (5HT) transporter inhibition with actions at 5HT receptors (5HT1A, 5HT1B, 5HT1D, 5HT7 receptors). *CNS Spectrums*; 20: 93-7.
9. Garnock-Jones KP. Vortioxetine: a review of its use in major depressive disorder. *CNS Drugs* 2014; 28: 855-74.
10. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol Ther* 2015; 145: 43-57.
11. Baldwin DS, Hanumanthaiah VB. Vortioxetine in the treatment of major depressive disorder. *Future Neurol* 2015; 10: 79-89.
12. Areberg J, Sogaard B, Hojer AM. The clinical pharmacokinetics of Lu AA21004 and its major metabolite in healthy young subjects. *Basic Clin Pharmacol Toxicol* 2012; 111: 198-205.
13. Lundbeck. Brintellix™ (vortioxetine hydrobromide tablets): US prescribing information. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf. Accessed 14 September 2015.
14. Lundbeck. Brintellix™ (vortioxetine tablets): EU summary of product characteristics. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/002717/WC500159449.pdf. Accessed 14 September 2015.
15. Hvenegaard MG, Bang-Andersen B, Pedersen H, Jørgensen M, Puschl A, Dalgaard L. 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: 1357-65.
16. Chen G, Lee R, Højer AM, Buchbjerg JK, Serenko M, Zhao Z. Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig* 2013; 33: 727-36.
17. Mork A, Pehrson A, Brennum L, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther* 2012; 340: 666-75.
18. 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: 3206-21.
19. 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. *Neuropharmacology* 2013; 73: 147-59.
20. Brown HS, Galetin A, Hallifax D, Houston JB. Prediction of in vivo drug-drug interactions from in vitro data: factors affecting prototypic drug-drug interactions involving CYP2C9, CYP2D6 and CYP3A4. *Clin Pharmacokinet* 2006; 45: 1035-50.
21. Lin JH. CYP induction-mediated drug interactions: in vitro assessment and clinical implications. *Pharm Res* 2006; 23: 1089-116.
22. Wang Y, Wojtkowski T, Hanson E, et al. An open-label, multiple-dose study in healthy adults to assess the drug interaction potential of Lu AA21004 using the Indiana cocktail. *J Clin Pharmacol* 2009; 49: 1114.
23. Chen G, Zhang W, Serenko M. Lack of effect of multiple doses of vortioxetine on the pharmacokinetics and pharmacodynamics of aspirin and warfarin. *J Clin Pharmacol* 2015; 55: 671-9.
24. Dalton SO, Sorensen HT, Johansen C. SSRIs and upper gastrointestinal bleeding: what is known and how should it influence prescribing? *CNS Drugs* 2006; 20: 143-51.
25. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. *Exp Opin Drug Metab Toxicol* 2014; 10: 721-46.
26. Boyer EW, Shannon M. The serotonin syndrome. *New Engl J Med* 2005; 352: 1112-20.
27. Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician* 2008; 54: 988-92.
28. Hansen DG, Rosholm JU, Gichangi A, Vach W. Increased use of antidepressants at the end of life: population-based study among people aged 65 years and above. *Age Ageing* 2007; 36: 449-54.
29. Trifirò G, Barbui C, Spina E, et al. Antidepressant drugs: prevalence, incidence and indications of use in general practice of Southern Italy during the years 2003-2004. *Pharmacoepidemiol Drug Saf* 2007; 16: 552-9.
30. Mark TL, Joish VN, Hay JW, Sheean DV, Johnston SS, Cao Z. Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs. *Am J Geriatr Psychiatry* 2011; 19: 211-21.
31. DeVane CL. Antidepressant-drug interactions are potentially but rarely clinically significant. *Neuropsychopharmacology* 2006; 31: 1594-604.
32. Schellander R, Donnerer J. Antidepressants: clinically relevant drug interactions to be considered. *Pharmacology* 2010; 86: 203-15.