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Review article

Vortioxetine: A review of the pharmacology and clinical profile of the novel antidepressant

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ABSTRACT

The aim of this paper was to review the up-to-date evidence base on pharmacology and clinical properties of vortioxetine.

Vortioxetine is a novel antidepressant, approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD). Because vortioxetine exhibits both an antidepressant and anxiolytic effect, it may be effective in treating both depressive and anxiety disorders, such as generalized anxiety disorder (GAD). Based on its pharmacodynamics profile and preclinical studies, it is believe that the drug's clinical action is mediated mainly by selective blockade of serotonin reuptake (by inhibiting the serotonin transporter [SERT]) and direct modulation of 5-HT receptors activity (such as 5-HT_3, 5-HT_7, 5-HT_{1D} and 5-HT_{1B}).

In patients with MDD the recommended doses range is 5–20 mg/day.

Vortioxetine was shown to be more effective than placebo both in MDD and GAD. In terms of side effects, nausea, vomiting, diarrhea, and dry mouth were most commonly observed in individuals receiving vortioxetine. In direct comparison to duloxetine, vortioxetine is found to have a smaller efficacy but had a lower risk of developing the common antidepressant-induced adverse effects.

Contents

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Introduction

Major depressive disorder (MDD) is a heterogeneous mental illness, with various biological and psychosocial underpinnings [1]. While biological background of MDD remains poorly defined, present theories focus on disturbances of neuroplasticity and neurotrophin signaling, the role of neuroinflammation, hyperactivity of hypothalamic-pituitary-adrenal axis, and – most notably – issues with monoaminergic neurotransmission [2]. The latter hypothesis, linking MDD to malfunctioning of serotonergic, noradrenergic and dopaminergic systems [3], remains the cornerstone of antidepressant drug development.

In this article we provide an overview of the pharmacology and clinical characteristics of vortioxetine – a novel antidepressant, acting both as a serotonin modulator and stimulator [2]. Vortioxetine was discovered by Lundbeck researchers (company code name: Lu AA21004) and then developed in partnership with Takeda Pharmaceuticals [7,20]. In 2013, the US Food and Drug Administration (FDA) and next the European Medicines Agency (EMA) approved vortioxetine for the treatment of MDD in adults [16,17]. The drug was first marketed as *Brintellix*®, but on May 2016, the US FDA approved a brand name change to *Trintellix*® in order to avoid confusion with the blood-thinning medicine *Brilinta*® (ticagrelor) [62]. The World Health Organization has issued an Anatomical Therapeutic Chemical (ATC) code for Trintellix that places it in the category of "Other" antidepressants. The drug is available for oral administration in doses ranging from 5 mg, 10 mg and 20 mg tablets.

For experimental pharmacology studies we searched the PubMed/MEDLINE repository, while Cochrane Library, Embase and PubMed/MEDLINE served as sources of relevant psychiatric data. In line with the framework of Evidence-Based Medicine (EBM) [4], in the clinical part of the analysis we included only randomized controlled trials (RCTs) and systematic reviews of corresponding RCTs comparing vortioxetine to other antidepressants or placebo. For the purpose of the literature searches, we used the following keywords: vortioxetine; Lu AA21004; bipolar*; depress*; MDD; cognitive funct*; anxiety*.

Pharmacology

Vortioxetine belongs to the class of bis-aryl-sulfanyl amines, and is chemically identified as 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (Fig. 1). The molecular weight and molecular formula for vortioxetine are 298.45 g/mol and $C_{18}H_{22}N_2S$, respectively. The mechanism of action of vortioxetine is considered to be related to its multimodal activity, i.e. selective blockade of serotonin reuptake (by inhibiting the serotonin transporter [SERT]) and direct modulation of serotonin (5-HT) receptors activity [6]. *In vitro* studies demonstrate that vortioxetine binds with high affinity to the SERT and some 5-HT receptors, such as 5-HT_3, 5-HT_7, 5-HT_{1D} and 5-HT_{1B} (for review, see Sanchez et al. [5]).

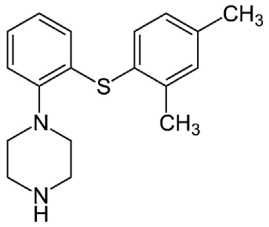

Fig. 1. The chemical structure of vortioxetine.

Pharmacodynamics. Receptor binding profile

Vortioxetine's receptor binding profile was characterized in a various *in vitro* binding and functional assays using recombinant cell lines (e.g. CHO cells and *Xenopus* oocytes), which express both human and rat targets. These studies showed that vortioxetine binds with high (only slightly lower than the reference escitalopram) affinity to the human (H_K_i = 1.6 nM) and rat (R_K_i = 8.6 nM) SERT, and may inhibit its activity, or serotonin reuptake (with the half maximal inhibitory concentration of 5.4 and 5.3 nM, respectively) [5,7]. In positron emission tomography (PET) studies in healthy volunteers, vortioxetine at a doses of 5, 10 and 20 mg/day demonstrated dose-dependent SERT occupancy rates in the brain, which was ~50, 53–65, and 80%, respectively for each dose [8]. It is currently believed that this property is the primary mechanism underlying the antidepressant effects of vortioxetine, as well as numerous other antidepressants [9].

The affinity of vortioxetine to other human neurotransmitter transporters, like norepinephrine (NAT) or dopamine (DAT) was a much lower (Ki = 113 nM and Ki >1000 nM, respectively). On the other hand, *in vitro* receptor binding studies demonstrated that vortioxetine also interacts with numerous 5-HT receptors [5]. This drug is a potent 5-HT_3 (H_K_i = 3.7; R_K_i = 1.8 nM) [7], as well as a weaker 5-HT_7 (H_K_i = 19 nM; R_K_i = 200 nM) and 5-HT_{1D} (H_K_i = 54 nM; R_K_i = 3.7) receptors antagonist. Furthermore, vortioxetine binds as a partial agonist to the human 5-HT_{1B} receptor (H_K_i = 33 nM; R_K_i = 16 nM) and as an agonist to 5-HT_{1A} receptor (H_K_i = 15 nM; R_K_i = 230) [5,7,10]. Except that, vortioxetine has affinity to the β1 adrenergic receptor (Ki = 46 nM), which is probably relevant only in the context of its side effects [7]. When tested against a panel of 70 other GPCRs, transporters, enzymes, ion channels and kinases, vortioxetine (1 μM) displayed no pharmacologically relevant activity [5].

The clinical implications of vortioxetine's action on serotonergic receptors are not known, but a number of potentially useful clinical effects have been attributed to some of these receptors. For example, agonism for the 5-HT_{1A} receptors may accelerate the clinical response. Activation of the somatodendritic 5-HT_{1A} receptors results in inhibition of serotonin neurons in raphe nuclei, leading to inhibition of the serotonin release and may cause delayed action of antidepressants with serotonin profile [11]. The use of 5-HT_{1A} receptor agonist, leads to a rapid somatodendritic receptors desensitization and disinhibition of serotonin release, activating post-synaptic 5-HT_{1A} receptors, which is associated with antidepressant activity [12]. In turn, the antagonism against 5-HT_7 receptor can promote the antidepressant effect of the drug occurring by inhibiting the reuptake of serotonin [13]. Particular importance is attributed to the influence of vortioxetine on 5-HT_{1B} and 5-HT_{3A} receptors. In an animal model, it was found that