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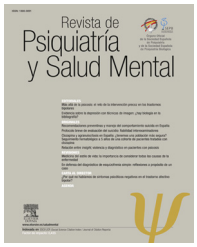

REVIEW ARTICLE

Vortioxetine: A new alternative for the treatment of major depressive disorder☆

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Abstract Major depressive disorder (MDD) is a serious psychiatric condition. Its treatment remains a challenge nowadays. Vortioxetine is a novel antidepressant with a unique profile, as it acts as a multimodal serotoninergic agent. Its efficacy in MDD has been established in many short- and long-term studies, with 7 positive, 4 negative and 1 failed randomized controlled trials. Moreover, its ability to modulate a wide range of neurotransmitters (serotonin, dopamine, norepinephrine, histamine, glutamate or GABA) confers vortioxetine pro-cognitive effects. Side effects are also different from conventional antidepressants, according to its low incidence of sexual dysfunction, weight gain or cardiovascular alterations. The aim of this systematic review is to describe the pharmacology, clinical efficacy and safety profile of vortioxetine, as well as its potential effectiveness in improving cognitive symptoms.

PALABRAS CLAVE
Vortioxetina;
Trastorno depresivo mayor;
Antidepresivo;
Cognición;
Receptores de serotonina

Vortioxetina: una nueva alternativa en el trastorno depresivo mayor

Resumen El trastorno depresivo mayor (TDM) es una enfermedad psiquiátrica grave cuyo tratamiento sigue siendo un reto en la actualidad. Vortioxetina es un nuevo fármaco antidepresivo con acción multimodal, lo que le confiere un perfil único. Su efectividad antidepresiva ha sido demostrada en varios estudios a corto y largo plazo, con 7 estudios aleatorizados positivos, 4 negativos y uno nulo. Además, su capacidad para modular varios neurotransmisores (serotonina, dopamina, noradrenalina, histamina, glutamato y GABA) le permite actuar sobre dominios

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como la cognición. Su perfil de efectos adversos es también distinto al de otros antidepresivos convencionales, dado que se relaciona con una baja incidencia de disfunción sexual, aumento de peso o alteraciones cardiovasculares. En esta revisión sistemática se describirán las características farmacológicas de vortioxetina y se detallará la evidencia disponible respecto a su eficacia clínica, su tolerabilidad y su prometedor efecto sobre los síntomas cognitivos.

Introduction

The lack of response to available antidepressant treatments remains one of the great challenges in psychiatry. Up to 1/3 of patients with major depressive disorder (MDD) do not achieve a complete response, and even in patients in remission, residual cognitive symptoms are commonly observed.[1–4] With this need in mind, and thanks to the advance in knowledge of the neural circuits involved in MDD,[5] molecules with a mechanism of action that goes beyond serotonergic activity are emerging.[6] The monoaminergic system, which includes the serotonergic, noradrenergic and dopaminergic pathways, is widely spread across the brain and it is known that this system and its multiple interconnections play an important role in mood disorders. This more integrative concept has motivated the search for drugs that will modulate the neurotransmitters involved in regulation of the monoaminergic system, such as glutamate or γ-aminobutyric acid (GABA).[7] Thus, the antidepressant, Vortioxetine, has recently been introduced on to the market. This drug is characterized precisely by its multimodal mechanism of action. In this systematic review, the pharmacological profile of Vortioxetine will be described; the available information regarding its clinical efficacy and safety will be detailed; and existing evidence will be thoroughly examined, focussing on its promising effect on cognitive symptoms.

Method

In order to identify studies focussed on the antidepressant, Vortioxetine, a systematic search of the literature was run. The search was conducted in November 2016 in Pubmed and ClinicalTrials.gov databases. The search terms used were ''Vortioxetine AND (''depression'' or ''depressive'' or ''action'' or ''effects'' or ''cognition'')'' for the Pubmed database and ''Vortioxetine AND depression'' for ClinicalTrials.gov. Preclinical articles were included to assess the effect of Vortioxetine in adults with MDD, published in English, with no date limit. The search was completed by manually reviewing the references of the first selected articles and review articles on the subject, which finally identified 221 articles of which 51 have been included. The selection process is described in detail in Fig. 1.

Pharmacological profile

Pharmacokinetics

Vortioxetine is absorbed slowly and has an absolute bioavailability of 75% after oral administration. Food does not influence its pharmacokinetics. The maximum plasma concentration is reached at 7–11 h and its half-life is 57 h.[8] It has a high plasma protein binding rate (96%)[9] and is widespread in peripheral tissues (volume of distribution: 2600 l).[10] Vortioxetine is metabolized in the liver through multiple isoenzymes of cytochrome P-450 (CYP450), such as CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6, with linear kinetics.[9,11] Its main metabolite is pharmacologically inactive and it is mostly excreted through the kidneys.[8] Stable plasma concentrations are reached at approximately 2 weeks and dose adjustment is not required for age, gender, renal disorders or in the case of mild-moderate hepatic dysfunction.[12]

Pharmacodynamics

Vortioxetine acts as an inhibitor of serotonin transporters (SERT) (Ki =1.6 nM) and regulates multiple subtypes of serotonin receptors (5HT): it acts as an agonist of 5HT1A receptors (Ki = 15 nM), partial agonist of 5HT1B receptors (Ki = 33 nM) and 5HT1D receptor antagonist (Ki =5.5 nM), 5HT3 (Ki =3.7 nM) and 5HT7 (Ki = 19 nM).[13–17] As reflected by affinity constants, Vortioxetine has a high affinity for SERTs[18] and 5HT3 receptors, so it must be taken into account that these receptors will be inhibited with low doses of Vortioxetine but high doses will be required to occupy all the receptors.[9]

Mechanism of action

Vortioxetine presents a unique and complex mechanism of action. Like conventional selective serotonin reuptake inhibitors (SSRIs), it is able to increase serotonin levels through the inhibition of serotonin transporters (SERTs). However, its action on the various subtypes of 5HT receptors gives it characteristic properties and has led to it being considered as a multimodal antidepressant. Fig. 2 summarizes the mechanism of action of Vortioxetine and its effects on various neurotransmitters.

5HT neurons abound in the brain, especially in the prefrontal cortex and the hippocampus—areas of the brain