Vortioxetine for generalised anxiety disorder in adults

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Abstract

Introduction

The currently accepted psychopharmacological treatment for generalised anxiety disorder in adults is associated with several adverse effects which threaten its acceptability. In this line, vortioxetine has been proposed as an alternative with less adverse effects in the treatment of this pathology.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified seven systematic reviews including five primary studies, all corresponding to randomized trials evaluating the effectiveness of vortioxetine in adult patients with generalized anxiety disorder without current treatment. We conclude that there is uncertainty whether vortioxetine increases the response to treatment or improves anxious symptoms, because the certainty of the existing evidence has been assessed as very low. Furthermore, vortioxetine may increase nausea (low certainty evidence).

Problem

Generalised anxiety disorder is a frequent mental illness characterised by persistent anxiety and worry about a wide variety of circumstances, accompanied by a series of physical and psychological symptoms [1]. Globally, generalised anxiety disorder implies a significant burden of disease, detriment of the quality of life and increased health costs [2].

According to the latest clinical practice guidelines, selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors are the first line of psychopharmacological treatment for generalised anxiety disorder in adults [3]. However, due to concerns about its effectiveness and the lack of adherence due to several associated adverse effects [4], new therapeutic strategies have been proposed, such as vortioxetine.

Vortioxetine is a multimodal antidepressant recently approved by the Food and Drug Administration and the European Medicines Agency for the treatment of major depressive disorder [4]. Its mechanism of action—partially elucidated—would be based on the direct modulation of different serotonergic receptors and on serotonin transporter inhibition [4]. Although there is little evidence about its efficacy, vortioxetine has been proposed as a promising alternative in the treatment of generalised anxiety disorder in adults.

Key messages

- We are uncertain whether vortioxetine increases response to treatment or if it reduces anxious symptoms as the certainty of the evidence has been assessed as very low.
- Vortioxetine may increase nausea (low certainty evidence).

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified seven systematic reviews [5], [6], [7], [8], [9], [10], [11] including five primary studies reported in seven references [12], [13], [14], [15], [16], [17], [18], all of which were randomised trials. One of the trials [18] was excluded because it analysed the long-term effectiveness of vortioxetine for generalised anxiety disorder in adults (i.e., relapse prevention), by including patients who had already been treated with vortioxetine in a previous open-label stage, for 20 weeks prior to randomisation.
What types of patients were included*	All the trials [12], [13], [14], [15] included patients older than 18 years with a diagnosis of generalised anxiety disorder, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria, without a current treatment. It should be noted that one of the trials [13] delimited the inclusion age up to 65 years. Each randomised trial [12], [13], [14], [15] included patients with greater than or equal score to 20 on the Hamilton Anxiety Rating Scale (HAM-A), and greater than or equal score to 2 in the first two items of the scale (i.e., anxious mood and tension). Similarly, patients with a total score of less than or equal to 16 on the Montgomery – Åsberg Depression Rating Scale were recruited in all the trials [12], [13], [14], [15]. All the trials [12], [13], [14], [15] excluded patients with other psychiatric comorbidities and/or other severe medical illnesses; patients with a recent history of substance abuse or suicidal ideation; and patients who have had a failed response to any previous treatment based on selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, correctly used (i.e., time and adequate doses) for the current anxiety episode.
What types of interventions were included*	In all the trials [12], [13], [14], [15] the use of oral vortioxetine once daily was compared with placebo. Two trials [13], [14] evaluated the use of vortioxetine 5 mg per day; one trial [15] assessed vortioxetine 2.5 mg once daily, 5 mg once daily and 10 mg once daily; and one trial [12] evaluated vortioxetine 2.5 mg per day and 10 mg per day.
What types of outcomes were measured	The trials evaluated multiple outcomes, which were grouped by the systematic reviews as follows:

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

	• Response to treatment (defined as greater than or equal reduction to 50% of the total score on Hamilton Anxiety Rating Scale initially measured). • Remission (defined as a total score less than or equal to 7 obtained in the Hamilton Anxiety Rating Scale at the end of the follow-up). • Anxious symptoms: change of the total score obtained initially in the Hamilton Anxiety Rating Scale, at the end of the follow-up. • Adverse effects (nausea*). The follow-up period in all the trials was eight weeks [12], [13], [14], [15]. * We considered 'nausea' for the 'adverse effects' outcome, due to missing data for total count of adverse effects.

* Information about primary studies is not extracted directly from primary studies but from identified systematic reviews, unless otherwise stated.

Summary of findings

Findings on the effects of vortioxetine for generalized anxiety disorder in adults are based on two randomised trials [12], [13] which included a total of 1238 patients.

This summary are based in two [12], [13] of the four randomised studies included (reported in six references) [12], [13], [14], [15], [16], [17], which evaluated the effectiveness of vortioxetine in adult patients with generalised anxiety disorder, without a current treatment. The above mentioned, because the rest of the trials did not evaluate the use of vortioxetine 10 mg per day, which we considered a matter of interest for the present summary, given their plausibility in clinical practice.

Both trials [12], [13] measured response to treatment (602 patients), adverse effects (nausea) (616 patients), and anxious symptoms (602 patients), comparing vortioxetine 10 mg once daily versus placebo. None of the included systematic reviews allowed data extraction that could be incorporated into a meta-analysis for the outcome remission.

The summary of findings is the following:

- We are uncertain whether vortioxetine increases response to treatment or if reduces anxious symptoms as the certainty of the evidence has been assessed as very low.
- Vortioxetine may increase adverse effects (nausea) (low certainty evidence).

Vortioxetine for generalised anxiety disorder in adults

Patients Adult patients with generalised anxiety disorderAdults
Intervention Vortioxetine 10 mg once daily
Comparison Placebo

Outcomes	Absolute*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT vortioxetine	**WITH vortioxetine**		
	Difference: patients per 1000			
Response to treatment	421 per 1000	433 per 1000	RR 1.03 (0.86 to 1.24)	⨁◯◯◯[1,2,3] Very low
	Difference:12 more (Margin of error: 59 less to 100 more)			
Adverse effects: nausea	130 per 1000	288 per 1000	RR 2.22 (1.56 to 3.17)	⨁⨁◯◯[1,2] Low
	Difference: 158 more (Margin of error: 73 less to 282 more)			
Anxious symptoms	11.17 points	10.56 points	--	⨁◯◯◯[1,2,3] Very low
	MD: 0.61 less (Margin of error: 1.15 less to 1.16 more)			

Margin of error: 95% confidence interval (CI).
RR: Relative risk.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

* The risk **WITHOUT vortioxetine** is based on the risk in the control group of the trials. The risk **WITH vortioxetine** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of evidence was downgraded one level due to undetermined risk of bias in domains «incomplete outcome data» in all included primary studies.
[2] The certainty of evidence was downgraded one level due to indirect evidence, because we considered "nausea" instead of total count adverse effects for this outcome (due to missing data). It should be noted that none of the primary studies compared vortioxetine with any currently accepted intervention (or any of its components) for the treatment of generalised anxiety disorder in adults (*e.g.*, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, psychotherapy, etc). Instead, all studies compared vortioxetine versus placebo.
[3] The certainty of evidence was downgraded one level due to imprecision because studies reported wide confidence intervals, carrying different effects.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

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* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The findings of this summary apply to adult patients with generalised anxiety disorder who have not received prior treatments for the current anxiety episode.

Our results do not apply to patients with psychiatric comorbidities (e.g., psychotic disorders, bipolar affective disorder, among others) or severe medical conditions (e.g., severe neurological disorders, among others).

Our results do not apply to patients with suicide risk (i.e., suicidal ideation or attempt) or with a history of substance abuse.

About the outcomes included in this summary

According to the authors' judgment, this summary includes critical outcomes for health decision-making (such as response to treatment or changes in anxious symptoms), which is reaffirmed by reports [19], [20] included in the Core Outcome Measures in Effectiveness Trials initiative (COMET) platform. However, according to the same studies [19], [20], new explorations that consider clinically relevant adverse effects (such as sexual dysfunction or increased body mass), and the social and/or occupational functioning, are needed.

Balance between benefits and risks, and certainty of the evidence

An adequate balance risk/benefit due is not possible due to the existing uncertainty of evidence regarding the decrease of anxious symptoms and the increase of the adverse effects (nausea) associated with vortioxetine. In fact, the evidence related to adverse effects associated with vortioxetine is controversial.

Among the adverse effects most frequently reported by the randomised trials included in this summary, were: nausea, dry mouth, diarrhea, constipation, anorexia, headache, dizziness, drowsiness, vomiting, among others.

Resource considerations

None of the included studies conducted a cost-effectiveness analysis. However, vortioxetine compared to first-line antidepressants used for generalised anxiety disorder in adults, is a high-cost drug, so its use would imply considerable resource expense. However, implementation of this alternative lacks support as long as the certainty of the evidence regarding to its effectiveness and acceptability remains unavailable.

What would patients and their doctors think about this intervention

As stated in a qualitative study [21], a prioritary point for patients who use antidepressants is finding a drug with minimal adverse consequences. Regarding first-line drugs for generalised anxiety disorder in adults, patients express much concern about sexual dysfunction and weight gain [21]. In this sense, emerging novel therapeutic options that promise another profile of adverse effects, such as vortioxetine, generate expectation.

According to the authors' opinion, therapists consider that greater certainty of the evidence is required to contemplate vortioxetine within the pharmacological arsenal for generalised anxiety disorder in adults. In turn, it should be noted that patients should be informed of the lack of evidence regarding the effectiveness and profile of adverse effects of vortioxetine, and its high cost compared to other recommended drugs with greater certainty of the evidence (such as the first line of treatment).

Differences between this summary and other sources

We detected some discrepancies among the findings of the systematic reviews identified in our comprehensive search [5], [6], [7], [8], [9], [10], [11], despite these included the same primary studies. This could be explained by the existence of methodological errors, presumably in data extraction. This is why new correctly developed systematic reviews are required, in addition to new randomised trials comparing vortioxetine with the first line of treatment.

The canadian clinical practice guidelines [3] suggest the vortioxetine as an alternative second-line psychopharmacological treatment for generalised anxiety disorder in adults. While in the german guidelines [22] and in the National Institute for Health and Care Excellence recommendations [23] its use is not recommended.

Could this evidence change in the future?

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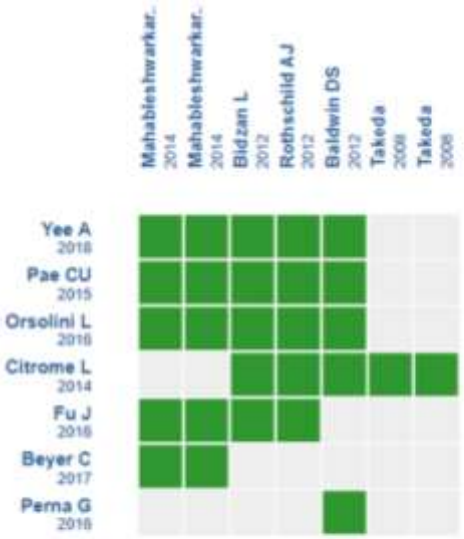
How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version** [Vortioxetine for generalised anxiety disorder in adults.]

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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