ROUND THE CORNER

VORTIOXETINE FOR DEPRESSION IN ADULTS - A REVIEW OF THE EVIDENCE FOR ITS CURRENT USE IN THE UK

Commentary on…Cochrane Corner

Riccardo De Giorgi
University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK
riccardo.degiorgi@bnc.ox.ac.uk

BIOGRAPHY

Riccardo De Giorgi is a Wellcome Trust Doctoral Training Fellow (DPhil in Biomedical and Clinical Sciences) at the University of Oxford, Department of Psychiatry and honorary MRCPsych Clinical Fellow at the Oxford Health NHS Foundation Trust. He works on experimental medicine trials in patients with treatment-resistant depression.

SUMMARY

The pharmacological treatment of depression is often hampered by side-effects and unsatisfactory response to treatment. Vortioxetine is one of the newest antidepressants on the market that promises to act on different mechanisms compared to other antidepressants. This month's Cochrane Corner review examines the evidence available for the first-line treatment of depression in adults with vortioxetine. This commentary puts the Cochrane review's findings into their clinical context and revises them in view of previous and later studies.

DECLARATION OF INTEREST

None.

PREVIOUS EVIDENCE

Vortioxetine is the latest antidepressant approved by the European Medicines Agency (EMA) (EMA 2014). The National Institute for Health and Care Excellence (NICE) recommends it in patients who have not responded to 2 antidepressants within the current episode (NICE 2015), a condition often defined "treatment-resistant depression" (TRD) (McIntyre 2014); however, this recommendation is based on a previous trial comparing vortioxetine with agomelatine (Montgomery 2014), indirect evidence from trials in drug-naïve patients, and experts' opinion. Intriguingly, the mechanism of action of vortioxetine is claimed as novel and related to the modulation of several serotonin receptors and the inhibition of the serotonin transporter (Sanchez 2015).

A large number of reviews - almost matching the number of trials of vortioxetine - had been published before the Cochrane review discussed here (Koesters 2017), but these were often flawed by methodological issues including the non-systematic design (i.e. the authors chose to include a subset of trials without defining any specific inclusion/exclusion criteria), the lack of pooled results (i.e. a meta-analysis of the data was not performed, thus it was not possible to draw conclusions on the basis of objective quantitative measures), or the conflict of interest (i.e. the drug's manufacturer had funded and therefore might have influenced the trials' results).

Therefore, the need for a systematic review and meta-analysis with more rigorous methodology was warranted.

SUMMARY OF THE COCHRANE REVIEW

The Cochrane review by Koesters *et al* (Koesters 2017) included 15 studies of 7'746 adults presenting with a first episode of depression. Vortioxetine was associated with response rates that were better than placebo and similar to serotonin-noradrenaline reuptake inhibitors (SNRIs), and with no differences in terms of patients leaving treatment.

DEFINITION OF THE CLINICAL QUESTION

The study aimed to assess whether patients with a first episode of depression respond (efficacy) and stay in treatment (acceptability) with vortioxetine more or less than either placebo or other antidepressants.

The trials' population included 7'746 participants above 18 years of age diagnosed with a first episode of depression according to the main international diagnostic criteria. Although patients with comorbid mental illness or suicidal ideation were not excluded *a priori*, none of the trials included this widely prevalent subgroup. In-patients and out-patients from a multinational setting were considered. Importantly, patients with TRD were excluded.

Any studies using vortioxetine as monotherapy were considered, but those employing dosages below the lowest effective dose of 5 mg/day were excluded. The comparison arms included placebo (14 studies) and SNRIs (8 studies). The review did not identify any trial (Box 1) comparing vortioxetine to any other class of antidepressants, notably SSRIs.

The primary outcomes were defined as efficacy or response to treatment (i.e. a reduction of at least 50% on any depression scale employed) and acceptability or number of patients staying in treatment (i.e. the inverse number of participants leaving the trial - drop-outs - for any reason), both measured at 6 to 8 weeks. Also, several secondary outcomes were measured; for example, drop-outs were divided between those leaving treatment for inefficacy and those leaving treatment because of adverse events.

METHODS

As per best practice when reviewing the effect of treatments, only randomised controlled trials were included.

The search strategy reviewed multiple electronic databases with no restrictions to date, language, or publication status. Inclusion and exclusion criteria were reflected by the search terms reported in the article. Then, the reference lists of the articles obtained were screened, and subject experts were contacted for information about ongoing or unpublished studies.

Two review authors independently screened the records for inclusion and, if required, resolved disagreements by consulting a third author. The whole process was appropriately reported in a flow diagram. Data regarding the trials' methods, population, intervention, comparison, outcomes, and funding or notable conflict of interest were extracted.

Likewise, the risk of bias was independently assessed by two authors, and reviewed with a third author if necessary, using the Cochrane Handbook for Systematic Reviews of Interventions criteria. Trials' biases were evaluated for randomisation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and funding. All trials had an "unclear" risk of bias (Box 2 and Risk of bias chart Figure 1) in at least two areas; remarkably, all studies were funded by vortioxetine's manufacturer, whereas the second area

varied across the different studies and included selection, performance, detection, and attrition biases.
The statistical analysis of data used risk ratios (RRs) with 95% confidence intervals (CIs) for measuring effect sizes.

RESULTS

Vortioxetine proved better than placebo in terms of response (RR=1.35, 95% CI 1.22 to 1.49) and was not different for the number of patients staying in treatment (RR=1.05, 95% CI 0.93 to 1.19). However, more patients dropped vortioxetine due to any adverse events (RR=1.41, 95% CI 1.09 to 1.81), whereas more people left the placebo arm because of inefficacy (RR=0.56, 95% CI 0.34 to 0.90).
In terms of the quality of the evidence, one-third of the studies showed a dropout rate above 20%, which negatively affected the significance of all the findings. Besides, the results for the efficacy outcome were very heterogenous, so the quality of this finding was further downgraded. The review authors did not comment on the precision of their pooled results, but the CIs were not particularly wide.
Overall, the clinical significance of these efficacy results remains uncertain. Although some authors maintain that all statistically significant differences in response rates are also clinically relevant (Montgomery 2009), this topic remains a matter of debate. The review authors calculated a number needed to treat for an additional beneficial outcome (NNTB) (Box 3) =8 (95% CI 5 to 12), meaning that a clinician would need to treat eight patients with vortioxetine rather than placebo in order to see one additional patient responding to therapy.

Moreover, vortioxetine was equivalent to SNRI for efficacy (RR 0.91, 95% CI 0.82 to 1.00), acceptability (RR 0.89, 95% CI 0.73 to 1.08), and patients' drop-outs for adverse events (RR 0.74, 95% CI 0.51 to 1.08) and inefficacy (RR 1.52, 95% CI 0.70 to 3.30).
In this case, however, the quality of the evidence was extremely low because two-thirds of the included studies showed a dropout rate above 20%, heterogeneity was high, and the CIs were very large and therefore imprecise. Hence, the clinical significance of these findings is difficult to interpret because of the very poor quality of the evidence supporting them.

DISCUSSION

In summary, this review showed that vortioxetine is better than placebo and equal to SNRIs for efficacy, and no worse than either in terms of acceptability. However, there are some important limitations.
Firstly, the trials' population only included patients who did not have any psychiatric comorbidity, suicidal thoughts, and had not been previously treated with antidepressants. This appears far from everyday clinical practice; hence, the external validity of the findings appears limited.
Furthermore, the most commonly prescribed first-line treatment for depression, namely SSRIs, are already known to have higher efficacy and acceptability than placebo in a primary care setting (Linde 2015). However, no studies comparing vortioxetine with SSRIs could be identified - a clear limitation to the applicability of this review's evidence. Most clinicians would argue that patients referred to specialist psychiatric services likely had not responded to one or more antidepressants beforehand, but this review excluded trials on TRD, further limiting the applicability of its results. Interestingly, the search strategy only identified one study of TRD patients comparing vortioxetine with agomelatine (Montgomery 2014); yet again

the clinical relevance of such comparison is poor for the UK practice, as agomelatine is scarcely used (NICE 2015).

CONCLUSION

Overall, it is questionable whether this study can influence clinical practice in the UK; however, it has highlighted some key questions that research needs to further explore, namely whether vortioxetine is better than SSRIs and whether vortioxetine is useful in TRD. Meanwhile, new evidence has been made available since the publication of this review.

The most recent and largest network meta-analysis (currently considered at the top of the evidence-base hierarchy) of antidepressants in adults identified an odds ratio (OR) for efficacy =1.66 (95% CI 1.45 to 1.92) and acceptability =1.01 (95% CI 0.86 to 1.19) when vortioxetine was compared to other antidepressants (Cipriani 2018).

Taking a different perspective, another recent review by McIntyre (McIntyre 2017) highlighted that vortioxetine has very low rates of side-effects commonly described for SSRIs such as sexual dysfunction, weight gain, and discontinuation effects, with nausea being the only adverse event reported in >10% patients; moreover, it has shown to prevent depressive relapses whilst remaining well-tolerated as long-term therapy. Patients frequently consider their overall functioning more important than symptom relief (Saltiel 2015). In this regard, manufacturers claimed that vortioxetine improves cognition and social relationships independently from mood scores (Lundbeck 2016), but the former have not been measured in this Cochrane's review.

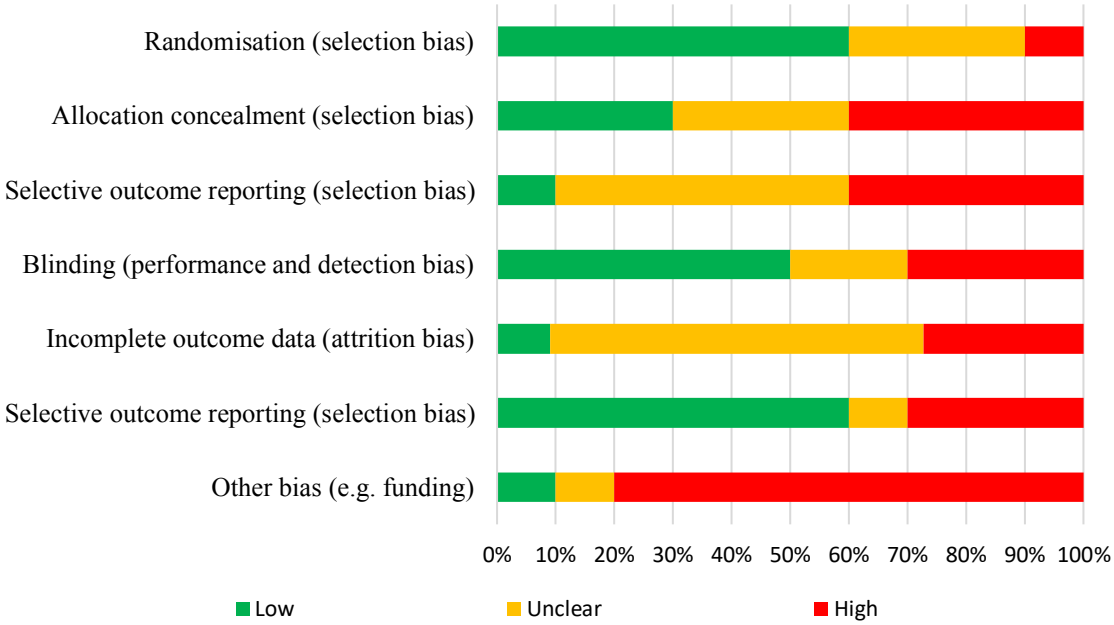
Oversea, the 2016 Canadian Network for Mood and Anxiety Treatments guidelines for depression included vortioxetine amongst first-line treatments (Kennedy 2015). Notably, the NICE guidelines for the UK (2015) on vortioxetine are due to be updated this year (2018) and may reflect some of the additional findings here reported.

BOXES AND FIGURES (underlined in the manuscript)

(Box 1) "Empty review": when a literature search for a systematic review retrieve no results, this is called an "empty review". Although this may be related to problems with the search strategy, sometimes an empty search is due to the lack of studies on a specific subject. Publishing an empty review may sound pointless; however, it is now considered important because it can highlight the absence of adequate research in some much-needed areas.

(Box 2) "Unclear" risk of bias: usually indicated by the amber colour, studies at "unclear" risk of bias sit between those at "high" (red colour) and "low" (green colour) risk of bias. The risk of bias may be unclear either because there are not enough details to differentiate between a "high" and a "low" risk, or because the risk remains unknown despite sufficient information being provided by the study authors.

(Figure 1) Risk of bias chart: an example of a risk of bias chart, which does not refer to the study commented here. The colour coding follows what described in (Box 2).



(Box 3) NNTB: the "number needed to treat for an additional beneficial outcome" (NNTB) is the same as the "number needed to treat" (NNT), defining the expected number of people who need to receive the intervention rather than the comparison for one additional person to develop the outcome in a given time frame. The opposite of the NNT is the "number needed to harm" (NNH); however, this term was considered unpleasant and misleading, thus the wording for the NNH was changed to "number needed to treat for an additional harmful outcome" (NNTH), and consequently the NNT was redefined as NNTB.

ACKNOWLEDGEMENTS

The author acknowledges the support of the Wellcome Trust [102176/Z/13/Z] and would like to thank Dr Kate Saunders, Prof Andrea Cipriani, and Prof John Geddes (University of Oxford, Department of Psychiatry) for their precious advice with this project. The views expressed are those of the author and not necessarily those of the Wellcome Trust or the NHS.

REFERENCES

Cipriani A, Furukawa TA, Salanti G, et al (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet, 391(10128):1357-1366

EMA (2014) Brintellix EPAR, public assessment report 2014. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002717/WC500159447.pdf

Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) (2016) Clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Can J Psychiatry, 61(9):540–560

Koesters M, Ostuzzi G, Guaiana G, et al (2017) Vortioxetine for depression in adults. Cochrane Database Syst Rev, 5;7:CD011520

Linde K, Kriston L, Rücker G, et al (2015) Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. Ann Fam Med, 13(1):69-79. doi: 10.1370/afm.1687

Lundbeck (2016) Pr TRINTELLIX® Vortioxetine (as vortioxetine hydrobromide) 5 mg, 10 mg, 15 mg, and 20 mg tablets, product monograph. https://www.lundbeck.com/upload/ca/en/files/pdf/pm/Trintellix.pdf

McIntyre RS, Filteau MJ, Martin L, et al (2014) Treatment-resistant depression: Definitions, review of the evidence, and algorithmic approach. Journal of Affective Disorders, Volume 156,1-7

McIntyre RS (2017) The role of new antidepressants in clinical practice in Canada: a brief review of vortioxetine, levomilnacipran ER, and vilazodone. Neuropsychiatr Dis Treat, 13:2913-2919

Montgomery SA, Moller HJ (2009) Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? International Clinical Psychopharmacology, 24(3):111–8

Montgomery SA, Nielsen RZ, Poulsen LH, et al (2014) A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum Psychopharmacol, 29(5):470-82

NICE (2015) Vortioxetine for treating major depressive episodes - technology appraisal guidance 2015. https://nice.org.uk/guidance/ta367

Saltiel PF, Silvershein DI (2015) Major depressive disorder: mechanism-based prescribing for personalized medicine. Neuropsychiatr Dis Treat, 11:875-88

Sanchez C, Asin KE, Artigas F (2015) Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther, 145:43-57