

1 ROUND THE CORNER

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

6 Commentary on...Cochrane Corner

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9 Riccardo De Giorgi

10 University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK

11 [riccardo.degiorgi@bnc.ox.ac.uk](mailto:riccardo.degiorgi@bnc.ox.ac.uk)

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14 BIOGRAPHY

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

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21 SUMMARY

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

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30 DECLARATION OF INTEREST

31 None.

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34 PREVIOUS EVIDENCE

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

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

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

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## 55 SUMMARY OF THE COCHRANE REVIEW

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

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## 62 DEFINITION OF THE CLINICAL QUESTION

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

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

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

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

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## 83 METHODS

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

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

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

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

100 varied across the different studies and included selection, performance, detection, and attrition  
101 biases.

102 The statistical analysis of data used risk ratios (RRs) with 95% confidence intervals (CIs) for  
103 measuring effect sizes.

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## 106 RESULTS

107 Vortioxetine proved better than placebo in terms of response (RR=1.35, 95% CI 1.22 to 1.49)  
108 and was not different for the number of patients staying in treatment (RR=1.05, 95% CI 0.93  
109 to 1.19). However, more patients dropped vortioxetine due to any adverse events (RR=1.41,  
110 95% CI 1.09 to 1.81), whereas more people left the placebo arm because of inefficacy  
111 (RR=0.56, 95% CI 0.34 to 0.90).

112 In terms of the quality of the evidence, one-third of the studies showed a dropout rate above  
113 20%, which negatively affected the significance of all the findings. Besides, the results for the  
114 efficacy outcome were very heterogenous, so the quality of this finding was further  
115 downgraded. The review authors did not comment on the precision of their pooled results, but  
116 the CIs were not particularly wide.

117 Overall, the clinical significance of these efficacy results remains uncertain. Although some  
118 authors maintain that all statistically significant differences in response rates are also clinically  
119 relevant (Montgomery 2009), this topic remains a matter of debate. The review authors  
120 calculated a number needed to treat for an additional beneficial outcome (NNTB) (Box 3) =8  
121 (95% CI 5 to 12), meaning that a clinician would need to treat eight patients with vortioxetine  
122 rather than placebo in order to see one additional patient responding to therapy.

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124 Moreover, vortioxetine was equivalent to SNRI for efficacy (RR 0.91, 95% CI 0.82 to 1.00),  
125 acceptability (RR 0.89, 95% CI 0.73 to 1.08), and patients' drop-outs for adverse events (RR  
126 0.74, 95% CI 0.51 to 1.08) and inefficacy (RR 1.52, 95% CI 0.70 to 3.30).

127 In this case, however, the quality of the evidence was extremely low because two-thirds of the  
128 included studies showed a dropout rate above 20%, heterogeneity was high, and the CIs were  
129 very large and therefore imprecise. Hence, the clinical significance of these findings is difficult  
130 to interpret because of the very poor quality of the evidence supporting them.

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## 133 DISCUSSION

134 In summary, this review showed that vortioxetine is better than placebo and equal to SNRIs  
135 for efficacy, and no worse than either in terms of acceptability. However, there are some  
136 important limitations.

137 Firstly, the trials' population only included patients who did not have any psychiatric  
138 comorbidity, suicidal thoughts, and had not been previously treated with antidepressants. This  
139 appears far from everyday clinical practice; hence, the external validity of the findings appears  
140 limited.

141 Furthermore, the most commonly prescribed first-line treatment for depression, namely SSRIs,  
142 are already known to have higher efficacy and acceptability than placebo in a primary care  
143 setting (Linde 2015). However, no studies comparing vortioxetine with SSRIs could be  
144 identified - a clear limitation to the applicability of this review's evidence. Most clinicians  
145 would argue that patients referred to specialist psychiatric services likely had not responded to  
146 one or more antidepressants beforehand, but this review excluded trials on TRD, further  
147 limiting the applicability of its results. Interestingly, the search strategy only identified one  
148 study of TRD patients comparing vortioxetine with agomelatine (Montgomery 2014); yet again

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

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## 153 CONCLUSION

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

158 The most recent and largest network meta-analysis (currently considered at the top of the  
159 evidence-base hierarchy) of antidepressants in adults identified an odds ratio (OR) for efficacy  
160 =1.66 (95% CI 1.45 to 1.92) and acceptability =1.01 (95% CI 0.86 to 1.19) when vortioxetine  
161 was compared to other antidepressants (Cipriani 2018).

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

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

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## 177 BOXES AND FIGURES (underlined in the manuscript)

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

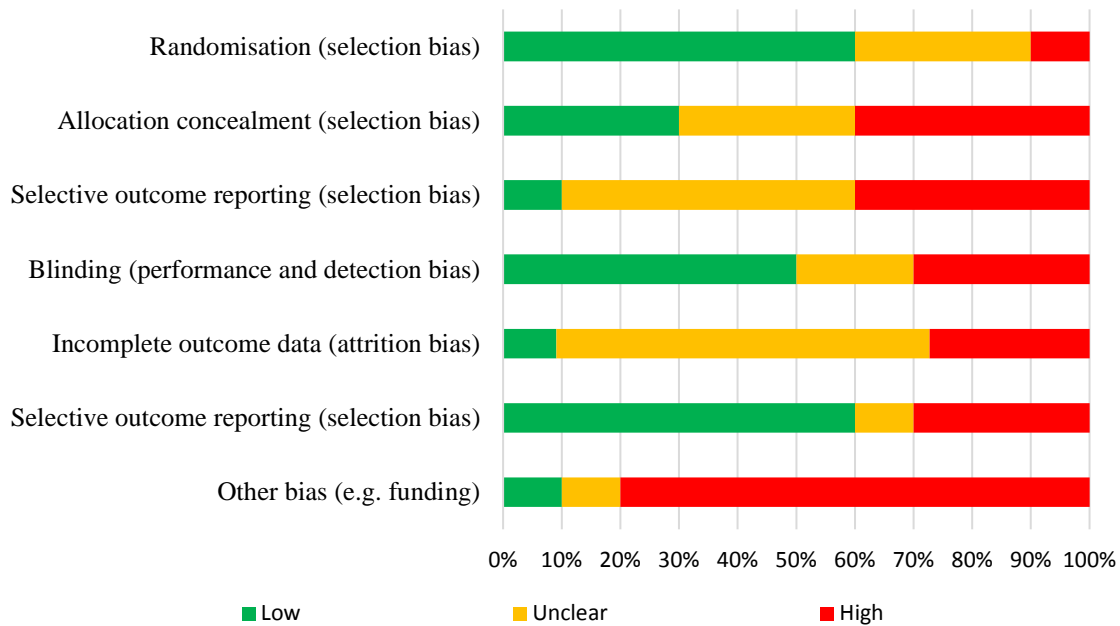
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184 (Box 2) “Unclear” risk of bias: usually indicated by the amber colour, studies at “unclear” risk  
185 of bias sit between those at “high” (red colour) and “low” (green colour) risk of bias. The risk  
186 of bias may be unclear either because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

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

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

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