Authors' reply: We would like to emphasise that our study included nationwide data on the use of all antidepressants in Denmark wherever prescribed (including from primary care), however nationwide data on the diagnosis of depression were only available from in-patient and out-patient psychiatric hospital settings (and not from primary care). Thus, as argued in our paper, we believe our findings can be generalised to all women taking antidepressants during pregnancy regardless of the indication for treatment (depression, anxiety disorder, etc.) or the severity of illness.

Although, the study included more than 34 000 women who used an antidepressant before or during pregnancy, this number was too small for separate analyses of the individual antidepressants divided into the eight risk groups defined in the study. Register-based medication studies at present do not have access to data on the dose of drug treatment or on patient adherence to the drug. We did try to adjust our analyses for physical disorder in the mother as all analyses were adjusted for all other types of medication (in addition to antidepressants) that the mother may have used during pregnancy, in this way taking account of treated physical and mental disorders as well as depressive and anxiety disorders. We further adjusted analyses for maternal age, employment status, smoking status, calendar year, parity, gender of the newborn, ±birth weight and ±gestational age, however we did not include data on nutrition of the mother and on obstetric complications as suggested. Obstetric complications may rather be intermediary factors than confounders.

Regarding the gestational age of all mothers, this was correctly indicated in Table 1 as a median of 39 (interquartiles 39–39), as infants with a gestational age less than 22 weeks were excluded from analyses and the vast majority of children were born within week 39.

Like Nebhinani & Soni, we hope the study will provide impetus for future research in this increasingly important area, especially as the use of antidepressants during pregnancy is believed to increase even further in the future.

Declaration of interest

L.V.K. has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZeneca, Pfizer, Wyeth, Servier, and Janssen-Cilag.

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Are the conclusions supported by the evidence?

Many people might be confused about the term 'placebo' that is used in Baxendale *et al*'s study.[1] The paper clearly refers to the low-intensity-light arm as receiving placebo treatment, and the clinical trial registration (http://clinicaltrials.gov/show/NCT01028456) also indicates that the low-intensity group is receiving a placebo. However, this has some implications for the interpretation of the results.

If the low-intensity arm is indeed a placebo, the active treatment group did not differentiate from placebo and this is, therefore, a negative study. If, however, the low-intensity arm is receiving an active treatment then there is no placebo group and we cannot determine whether any changes in symptoms were due to the treatment or would have occurred by chance.

The conclusions that light therapy may 'be an effective treatment for symptoms of low mood in epilepsy at lower intensities than those typically used to treat seasonal affective disorder' cannot be supported by the findings of this study, since there was not an adequate control group. Further, the authors acknowledge that a number of non-specific factors may account for any improvements in depression and anxiety and all participants received relaxation. I strongly suspect that the fact that the participants had their eyes open during relaxation does not negate the effects on anxiety that relaxation training might have. In addition, most of the improvement in both groups (particularly on the depression subscale) had occurred before they were exposed to the intervention, i.e. at T_2.

The clinical trial registration indicates that the control arm should have been receiving 100 lux for 30 min a day and the active arm 10 000 lux for 30 min a day. The study suggests that both arms received 20 min of light per day, with the control arm receiving an intensity of 2000 lux. It is not clear why the intensity was increased.

The attrition rate was high in both groups: 18/45 (40%) in the control arm and 15/46 (32.6%) in the active arm. Five patients in the active arm had an increase in seizures or required their medication to be increased (compared with two patients in the control arm). In the other paper emerging from this study,[2] the authors caution about using bright light in this population because 'it may result in an increase in seizures for some'. None of this caution is evident in the paper published in the *British Journal of Psychiatry*. Indeed, there is not a single mention of adverse effects, despite them being reported elsewhere.

The analysis does not appear to have been intention-to-treat, and the results are only reported for those patients that completed the trial. This is a significant weakness when the authors have reported the possibility of adverse effects in other journals and when the attrition rates are relatively high. It is not clear why this intervention in an epilepsy population is treated with some reservations, yet it is reported much more favourably when there are some improvements in a secondary outcome measure reflecting some aspects of mental health (anxiety and depressive symptoms) which occurred before the intervention.

1 Baxendale S, O'Sullivan J, Heaney D. Bright light therapy for symptoms of anxiety and depression in focal epilepsy: randomised controlled trial. *Br J Psychiatry* 2013; **202**: 352–6.

2 Baxendale S, O'Sullivan J, Heaney D. Bright light therapy as an add on treatment for medically intractable epilepsy. *Epilepsy Behav* 2012; **24**: 359–64.

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Author's reply: Dr Christmas is quite correct in reiterating the uncertainty we expressed in our discussion about the placebo condition in our study. This does indeed have very significant implications for the interpretation of our results. It is for this reason that we suggested a number of different interpretations for our findings in the Discussion, including the possibility that light therapy 'may, therefore, be an effective treatment for symptoms of low mood in epilepsy at lower intensities than those typically used to treat seasonal affective disorder'. We also discussed the possibility that this could indeed be a negative finding or that the results we found could be due to other factors unrelated to light therapy, such as the establishment of fixed morning routines.

Dr Christmas is correct in that in the original protocol for the study the control arm should have been receiving 100 lux. The modifications to the original protocol were submitted with the paper as an online appendix, to conform to the CONSORT

guidelines for reporting trials. In this case, when the light boxes were modified to 100 lux, the disparity in intensity was very obvious and we did not feel that the study would conform to the important double-blind aspect of the design. It would have been very clear to any patient who received the 100 lux box that they had been assigned to the low-intensity arm of the trial. We therefore modified the boxes to administer 2000 lux at 20 min in the low-intensity arm. The boxes appeared bright, but literature on seasonal affective disorder indicates that this would not be a therapeutic dose within this time frame, whereas 10 000 lux at 20 min would be a therapeutic intensity/dose.

As we stated in the introduction to our study, the primary outcome measure for this trial was seizure control. We have reported these results separately[1] and that paper is fully referenced in our study. Although it is possible that bright light therapy may result in an increase in seizures for some patients, this was not a statistically significant finding in our previous study and, as yet, the risk remains theoretical. Clinicians will be aware that seizure control should be carefully monitored following the introduction of any new treatment offered to people with epilepsy.

In presenting the results of our study for publication we have sought to provide as clear an account of the data as possible. The results are by no means clear-cut or definitive. However, there are some interesting aspects to the data that suggest that this may not be a dead end in terms of a treatment option for some people with epilepsy. This study stands as a guide for future research. We hope that its limitations, which we fully acknowledge and have set out at length in the Discussion, will serve as a useful guide for future research in this area.

1 Baxendale S, O'Sullivan J, Heaney D. Bright light therapy as an add on treatment for medically intractable epilepsy. *Epilepsy Behav* 2012; **24**: 359–64.

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Results for behavioural activation are overstated

The study by Moradveisi *et al*,[1] which is applicable to both secondary mental health and primary care, looks at the prospect of using minimally trained staff in delivering behavioural activation against pharmacological intervention in the treatment of severe depression. We would like to highlight the following points for further clarification.

First, an obvious problem of the study was the lack of a placebo arm, which would have lent credibility. As the cultural avoidance of antidepressants in Iran has been highlighted, adding a placebo group would have removed some bias such as paying for medication in the treatment as usual (TAU) group after 3 months and also in the analysis.

Second, sertraline was used at a suboptimal dose and was slowly titrated, against prevailing practice. A meta-analysis shows an optimum dose for sertraline between 100 and 150 mg/day – doses below the therapeutic range were significantly less effective, i.e. by 7%.[2] Sertraline reached its lowest therapeutic dose of 100 mg at 6 weeks. All drop-outs occurred before the mid-point assessment and only three were as a result of medication side-effects.

Third, there was a significant difference in the amount of attention that participants received in each group. Participants in the behavioural activation group received 50% more face-to-face sessions than the TAU group. The study did not adjust for this in the analysis.

Fourth, last observation carried forward (LOCF) was used in the study. However, 5% of drop-outs occurred in the behavioural activation group as opposed to a significant 30% from the TAU group. Last observation carried forward is used frequently in intention-to-treat studies but standard errors and confidence intervals from LOCF underestimate uncertainty.[3] As there are no strategies for universal use, reasons for the choice of a certain method have to be provided when designing and analysing clinical trials.[4] Last observation carried forward analysis seems to have favoured the behavioural activation group.

Many other limitations of the study are cited in the paper itself. Significant numbers of participants were recruited via advertisement or word of mouth, which seemed to have attracted more women and perhaps more psychologically minded individuals. It would have been helpful to include these advertisements as a supplement to the paper in order to identify any bias.

Finally, we wondered whether an ethics committee would allow this type of study to go ahead in the UK as it included individuals with severe depression. In England and Wales, before recruitment to a trial, potential participants must be assessed under the Mental Capacity Act 2005; in Scotland, the Adults with Incapacity (Scotland) Act 2000 (para. 72) must be used.[5] Since the authors of the study state that 'the study's aim was to investigate whether a simple psychological treatment [. . .] would be a viable alternative to antidepressant medication [. . .] in a non-Western country', we are unsure of an equivalent law in Iran and whether this criterion was met.

1 Moradveisi L, Huibers MJH, Renner F, Arasteh M, Arntz A. Behavioural activation v. antidepressant medication for treating depression in Iran: randomised trial. *Br J Psychiatry* 2013; **202**: 204–11.

2 Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants. Meta-analysis of dose–effect relationships in randomised clinical trials. *Br J Psychiatry* 1999; **174**: 297–303.

3 Mallinckrodt C, Clark W, David S. Accounting for dropout bias using mixed-effects models. *J Biopharm Stat* 2001; **11**: 9–21.

4 Unnebrink K, Windeler J. Intention-to-treat: methods for dealing with missing values in clinical trials of progressively deteriorating diseases. *Stat Med* 2001; **20**: 3931–46.

5 General Medical Council. *Consent: Patients and Doctors Making Decisions Together*. GMC, 2008.

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Authors' reply: We thank Kripalani & Suleman for their critical remarks. Before addressing them point by point, a general remark is required. Our trial was an effectiveness, not an efficacy, trial. We compared a new treatment previously tested elsewhere (behavioural activation) with treatment as usual (TAU) (antidepressant medication) in Iran. An effectiveness trial aims to assess outcomes in usual care, not to test specific mechanisms, which affects the type of control condition(s). Some criticisms make sense from an efficacy study point of view, not from an effectiveness study point of view. Also of note is that the initial response to TAU was quite good, and that the longer-term response of behavioural activation accounted for its superiority.

We do not see how a placebo arm could have assessed cultural influences on TAU. To study this interesting topic, both a placebo and a natural course condition are needed to see whether placebo in Iran does worse than in other cultures compared with doing nothing.

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