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Good news regarding SSRI safety in Danish meta-analysis

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Abstract

In two previous letters on an *selective serotonin reuptake inhibitor* (SSRI) meta-analysis conducted by the Copenhagen Trial Unit at Copenhagen University Hospital, we have commented on a large number of errors, almost all of which have tilted the results in an anti-drug direction, that unfortunately mar this publication. While the authors have acknowledged many of these mishaps, and may now be expected to submit an extensive errata list to the journal where their paper was once published, we regretfully note that also their latest contribution to this exchange is surprisingly inaccurate. However, its many shortcomings notwithstanding, their meta-analysis does add to the current literature by confirming that SSRIs do not seem to enhance the risk for suicide or death, and also that these drugs seem to enhance the risk of side effects categorised as serious only in the elderly.

Commentary

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We thank Katakam and co-workers for responding to our most recent comment (Hieronymus *et al.*, 2018a) on their SSRI meta-analysis published in *BMC Psychiatry* (Jakobsen *et al.*, 2017a). When summarising this exchange, we are pleased to note that the Copenhagen Trial Unit (CTU) group do *not* question our remark that neither suicide nor death of any other cause was more common in patients on SSRIs in their huge database (Katakam *et al.*, 2019). In fact, both suicide and death of any cause were – though not significantly so – *less* common in patients on SSRIs (Hieronymus *et al.*, 2018b). And we are similarly pleased to note that they, in their final rebuttal, acknowledge that a significantly higher frequency of serious adverse events (which may or not may be truly serious, see Hieronymus *et al.*, 2018b) was only found in the elderly (Katakam *et al.*, 2019), which is well in line with previous studies.

While we unfortunately have had reasons to criticise various aspects of their study, we do admit that it is sufficiently comprehensive to enable the authors to detect an increase in suicide in subjects treated with SSRIs in clinical trials if such an effect were at hand. Unlike the impression given by Janus Christian Jakobsen when touring Scandinavian media, an important take-away message of their extensive study, on which the authors in fact now seem to agree (Katakam *et al.*, 2019), hence is that *there is no evidence indicating that SSRIs enhance the risk for suicide or death of any cause*, and also that *no evidence has been found for these drugs enhancing the risk of serious adverse events in the non-elderly*. Since SSRIs are often attributed harmful effects, Jakobsen and co-workers should be congratulated for adding this reassuring piece of information to the preexisting bulk of evidence on these important matters. Of note is that an extensive umbrella review recently confirmed the data from Jakobsen and co-workers by concluding that antidepressants appear to be safe to use for the treatment of psychiatric disorders (Dragioti *et al.*, 2019).

With respect to the numerous errors that we have identified in their paper (Hieronymus *et al.*, 2018a, b), many of which the authors acknowledge, and some of which they deny (Katakam *et al.*, 2018, 2019), we realise that this exchange since long must have exhausted the patience of the readers of *Acta Neuropsychiatrica*. While we do not at all agree with the claims made in their most recent contribution to this exchange (Katakam *et al.*, 2019), we will hence refrain to rebut them one by one in this reply (that will be our final). However, to provide a few examples of why we find also the last rebuttal from Katakam and co-workers disappointing, we may just mention that (i) they have still not apprehended that one cannot expect trials conducted and published over a decade before the *International Committee on Harmonization-Good Clinical Practice* guidelines were published (Otte *et al.*, 2005) to adhere to these guidelines, (ii) they still seem not to have realised that they have been inconsistent in their handling of treatment groups and events (as in the cases of Pettinatti *et al.* and Adamson *et al.*; for refs, see Hieronymus *et al.*, 2018a), (iii) they fail to acknowledge, in spite of the examples we have provided, that many trials do not explicitly detail serious adverse events (SAEs) in the placebo group (for refs, see Hieronymus *et al.*, 2018a, b), (iv) they still seem not to realise that they should not have excluded the results of the Egger test after realising that the outcome was not what they had hoped

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for (i.e. indications of publication bias), when it instead suggested a potential problem with their literature search, (v) they are mistaken when claiming that they have divided the placebo group in study SCT-MD-01 by three, as they should have, but have not, and (vi) they have still not realised that pre-sleep values in the paper by Jindal et al. refer to pre-treatment values, which should be obvious to anyone inspecting Tables 1 and 2 in this publication (Jindal *et al.*, 2003). Likewise, a friendly advice to the CTU group is that it is recommendable to read the paper one references for a statistical analysis (such as the publication by Sweeting; for ref, see Hieronymus *et al.* 2018b), rather than a one-sentence-summary of the method provided in the Cochrane handbook, since one otherwise runs the risk of implementing the method incorrectly, as they have done. Instead of making this list any longer, we invite any reader to contact us by e-mail for further clarifications on this and other matters where we believe that the CTU group, also in their latest rebuttal, have gone astray.

Shortly after publishing their paper in *BMC Psychiatry*, the authors commendably reported a number of minor errata in the same journal, such as a misspelling of 'Nemeroff' and 'fluoxetine' (Jakobsen *et al.*, 2017b). We have respectfully suggested that the large number of considerably more important errors since then disclosed by us, and acknowledged by the authors, would justify a retraction of this paper (Hieronymus *et al.*, 2018a), but realise that this will not happen (Katakam *et al.*, 2019). Instead we assume that the authors will now hurry to submit a new and comprehensive list of errata to the journal.

We would finally like to add a few words regarding bias. On the one hand, the authors claim that there is a 'high risk of bias' for *all* trials they have analysed, one important reason being that most of them were industry-sponsored. And on the other hand, they make the following claim in the summary of their most recent contribution: 'Our analysis should be impartial and free from any biases and prejudices as we do not have any obligations to support the interests of sponsors or other groups' (Katakam *et al.*, 2019). We do not share this view.

First, it should be noted that the influence of the drug companies on the outcome of their own trials is vastly exaggerated. There has clearly been a tendency for companies to refrain from publishing negative trials, and for making the most of the positive ones, and sometimes for choosing doses of comparators to make their own drug look good; such aspects are however all easy to adjust for when conducting company-independent post hoc analyses (where also the non-published trials are usually possible to identify and include). But since drug trials are closely monitored and regulated, the companies can hardly tamper with the data even if they so wanted. The high rate of putative antidepressants that have failed during the clinical development phase and hence never reached the market, prompting many of the large pharmaceutical companies to abandon the field of psychiatry (Wegener *et al.*, 2013), bears witness to the inability of the drug companies to present ineffective and intolerable antidepressants as were they effective and tolerable. The policy of CTU and like-minded to regard all trials sponsored by a company as being at high risk of bias is hence misleading. Of note in this context is that Munkholm and co-workers in a recent SSRI-critical meta-analysis (Munkholm *et al.*, 2019) noted higher effect sizes for antidepressants in company-independent trials than in those conducted by the drug industry.

Furthermore, it is naïve to assume that contributions from workers that 'do not have any obligations to support the interests of sponsors or other groups' (Katakam *et al.*, 2019), such as Drs. Katakam, Sethi, Jakobsen, and Gluud, are per definition free from bias. There are hence numerous factors – such as wanting to confirm an idea that one cherishes, the wish for a prosperous scientific career, or a desire to make a splash in Danish media – that may bias how a researcher interpret and present his/her data.

A general anti-pharma stance is another such factor that unfortunately is particularly abundant in the field of psychopharmacology. There is much to be said – both good and bad – about the drugs used in psychiatry, but for a number of debaters and researchers in the field, the undisputed starting point seems to be that psychopharmacological agents per definition are both ineffective and harmful, and that anyone claiming otherwise must be bribed by Big Pharma. We do not share this view, and do not believe it will aid to advance the field.

With respect to the CTU, there is also an additional source of potential bias. This unit is hence funded directly by the Danish state *inter alia* to conduct independent meta-analyses (Copenhagen Trial Unit), the underlying belief obviously being that they will provide relevant information beyond what the pharmaceutical industry and the scientific community would otherwise produce. Had they not regularly demonstrated their alleged importance by publishing data at odds with conventional wisdom, as has been the case with respect to the SSRIs and the drugs against hepatitis C, their *raison d'être*, and hence their funding, might be rightfully questioned. Thus, every time the CTU researchers tout the bias and lack of reliability in reports from the pharmaceutical industry, or the incompetence of other scientists than themselves, they pave the way for the future funding of their own salaries (Copenhagen Trial Unit).

The SSRIs are far from perfect drugs: they are probably not as effective (but more tolerable) than some of the older antidepressants, it takes many weeks for the effect to be full-blown, a considerable portion of subjects do not respond, they do have some common (though reversible) side effects, and some patients may react negatively when exposed to them, for example, with enhanced anxiety. But these drugs do display a clear-cut antidepressant effect (with an effect size well on par with drugs used for somatic conditions) (Hieronymus *et al.*, 2016) and they are, by and large, safe. Had the CTU group been less biased, they would have realised that this is confirmed by their own (though somewhat shaky) data.

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