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RESPONSE TO LETTER

Appropriate Outcome Choice Requires Certainty About Symptom Patterns of Patient Subgroups – We are Still Left with Unexplained Heterogeneity [Response To Letter]

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Dear editor

With great interest I read the letter by Wessa et al.[1] The authors conducted subgroup meta-analyses on randomized controlled trials (RCTs) and observed a superior efficacy of the anti-inflammatory treatments celecoxib (CXB) and minocycline (MCO) over placebo when the Hamilton Depression Rating Scale (HAMD) was used as an outcome measure, but not when the Montgomery–Asberg Depression Rating Scale (MADRS) was used.[1] This notion is critical regarding two aspects:

1. the judgement of the strength of evidence from the reviewed meta-analyses by heterogeneity, ie, the evidence for MCO was judged as less strong than for CXB where outcome scales were combined (MCO) as compared to the sole use of HAMD (CXB);[2]
2. the interpretation of efficacy and conclusions drawn for clinical practice, ie, when outcomes scales include a different set of symptoms the clinical benefit of a treatment is difficult to attribute.

Further, the meta-analyses reviewed by Simon et al did not incorporate recently published RCTs since they had not yet been available.[2] Considering these aspects, Wessa et al point out important shortcomings in research up to now.[1]

However, the issue seems more complex and should be discussed even further. Arguing that the HAMD may be the more appropriate outcome measure to capture anti-inflammatory treatment efficacy while arguing that the HAMD was not designed to assess disease severity seems somewhat contradictory.[1] Further, according to the original description of the HAMD, it is used for quantification and items not measuring depression or its intensity were excluded from the scale, thus allowing the conclusion that it was designed to assess disease severity after all.[3]

If the HAMD assessed the presence of symptoms only the question arises of whether its total score is an appropriate measure for treatment success at all. In that case it could be more useful to identify patient subgroups (like the proposed somatic/neurovegetative subtype) and to stratify patients before anti-inflammatory treatment application. However, in this subgroup the core psychological symptom of depressed mood was associated with inflammatory markers, also.[4] Whether the improvement by anti-inflammatory treatments is specific to certain symptoms is not known so far and would require an item-based evaluation. Thus, the idea that anti-inflammatory treatment may be effective for somatic/neurovegetative symptoms but not for other symptoms (mainly assessed by the MADRS) is a matter of speculation to explain the different study results for both scales, despite it being a valid consideration.

In one recent publication evaluating efficacy of MCO over placebo, differences of symptom change between both arms were calculated for the MADRS but also for the HAMD.[6] For both scales, no significant difference emerged.[5] This

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makes two out of actually four studies mentioned by Wessa et al showing no superiority of MCO using the HAMD.[1] Taking up another example of a recent publication evaluating efficacy of CXB over placebo, both treatment arms resulted in high response rates of 57.9% and 69.6%, respectively, using the MADRS.[6] Even though superiority of CXB could not be demonstrated, it still shows that a large clinical improvement could be detected using the MADRS.[6] RCTs using the HAMD as outcome consistently reported a difference in response rates between the CXB and placebo arms, ie placebo response rates were (much) lower in those studies.[7–10] Further, response rates varied considerably between the studies but were at least partly in the range of the MADRS study.[7–10] Therefore, other factors apart from the outcome scale itself likely play a role for the given results, also.

As mentioned by Simon et al, heterogeneity due to combined outcome scales in the reviewed meta-analyses contributes to uncertainty of evidence on the efficacy of anti-inflammatory treatments for depression.[2] Conducting subgroup analyses by outcome, as proposed by Wessa et al, can help disentangling the multifactorial problem.[1] Future studies should evaluate the MADRS and HAMD as outcomes to get a better impression of the differences between both for efficacy measurement. To judge the appropriateness of the outcome scale also requires a better understanding of the actual characteristics of patient subgroups that may profit from anti-inflammatory treatments. As a future perspective, Simon et al stress that patient stratification by immune profiles should be done before treatment application to actually target specific patient subgroups.

Disclosure

The author declares no potential conflicts of interest in this communication.

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