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LETTER

Choice of Outcome Measure Predicts Anti-Inflammatory Treatment Efficacy in Major Depressive Disorder [Letter]

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Dear editor

We are writing to bring to your attention a noteworthy observation we made while examining the results of the Randomised Controlled Trials (RCTs) that evaluated the efficacy of anti-inflammatory or immune-targeted treatments in Major Depressive Disorder (MDD). We read the meta-review on this topic by Simon et al[1] with great interest and found it to be a valuable summary of the current evidence. The meta-analytic evidence, particularly regarding to Minocycline (MCO) and Celecoxib (CXB) being the most effective compounds, holds promising prospects for future antidepressant treatment guidelines.

Upon review of the results of the individual RCTs, we however noticed that the use of the Montgomery-Åsberg Depression Rating Scale (MADRS) versus the Hamilton Depression Rating Scale (HAMD) as the outcome measure seemed to have an impact on the results.

Table 1 and Table 2 illustrate these observations by presenting the findings from RCTs that used the MADRS and HAMD as primary outcome measures to assess the antidepressant effect of either MCO or CXB. We also incorporated recently published RCTs not included in the previous meta-analyses. The RCTs using the MADRS as primary outcome measure resulted in negative outcomes, while the trials using the HAMD produced positive results. This difference was statistically significant in a random-effects meta-analytic subgroup analysis we performed in CMA v.3.3.070 (total between-groups MCO Q=8780; df=1; p=0.003; CXB Q=17,0; df=1; p<0.001; forest plots shown in Figures 1 and 2).

This difference is likely due to the design of the two measurement scales. The HAMD was not designed to measure the severity of depression but rather to assess different depression symptoms,[2] while the MADRS was designed to measure the severity of depression and does not capture the somatic or neurovegetative symptoms.[3] As a subtype of depression, immune-mediated depression is associated with these somatic or neurovegetative symptoms, sparking the hypothesis that immunomodulatory treatments may be more effective in treating these symptoms.[4]

This matter becomes even more pertinent given the choice of Simon et al not to include studies using the MADRS in their analysis for CXB. Our results indicate that adding these studies renders the overall effect of adjunctive CXB non-significant (Table 2).

In light of these findings, it is crucial to consider the suitability of the outcome measure when evaluating the efficacy of immunomodulatory treatments for MDD. The use of the HAMD, which captures a wider range of

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Table 1 Standardised Mean Differences and 95% Confidence Intervals for Randomized Controlled Trials Evaluating the Efficacy of Minocycline in Depression Treatment Using HAMD and MADRS Outcome Scales

MCO Study	Outcome Scale	MCO	PBO	SMD	Lower Limit	Upper Limit
Emadi-Kouchak et al, 2016	HAMD	N=23	N=23	1.060	0.457	1.663
Husain et al, 2017	HAMD	N=21	N=20	1.090	0.383	1.797
Nettis et al, 2021	HAMD	N=18	N=21	0.504	−0.135	1.144
HAMD, p-value<0.001				0.879	0.506	1.253
Dean et al, 2017	MADRS	N=36	N=35	0.370	−0.092	0.832
Helmann-Regen et al, 2022	MADRS	N=81	N=87	0.154	−0.248	0.358
MADRS, p-value=0.277				0.162	−0.130	0.455
Total, p-value<0.001				0.435	0.205	0.665

Abbreviations: HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; MCO, minocycline; PBO, placebo; SMD, standardized mean difference.

Table 2 Standardised Mean Differences and 95% Confidence Intervals for Randomized Controlled Trials Evaluating the Efficacy of Celecoxib in Depression Treatment Using HAMD and MADRS Outcome Scales

CXB Study	Outcome Scale	CXB	PBO	SMD	Lower Limit	Upper Limit
Müller et al, 2006	HAMD	N=20	N=20	0.710	−0.224	1.644
Akhondzadeh et al, 2009	HAMD	N=20	N=20	0.730	0.110	1.350
Abbasi et al, 2012	HAMD	N=20	N=20	0.930	0.039	1.821
Majd et al, 2015	HAMD	N=14	N=9	0.580	−0.226	1.386
Jafari et al, 2015	HAMD	N=20	N=20	2.020	1259	2782
HAMD, p-value<0.001				1.001	0.469	1.534
Baune et al, 2021	MADRS	N=59	N=60	−0.300	−0.656	0.056
Simon et al, 2021	MADRS	N=20	N=23	−0.275	−0.877	0.327
MADRS, p-value=0.061				−0.293	−0.600	0.013
Total, p-value<0.001				0.029	−0.237	0.295

Abbreviations: HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; CXB, celecoxib; PBO, placebo; SMD, standardized mean difference.

depression symptoms, may provide a more accurate reflection of the benefits of these treatments. Similarly, meta-analyses synthesizing the available evidence should differentiate between these outcome measures in subgroup analyses.

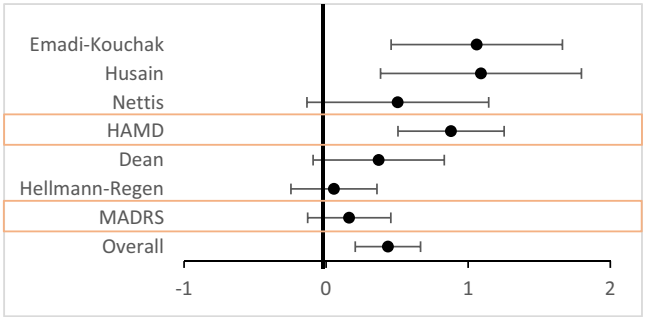

Figure 1 Forest plot of standardised mean differences and 95% confidence intervals for randomized controlled trials evaluating the efficacy of minocycline in depression treatment using HAMD and MADRS outcome scales.
Abbreviations: HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; MCO, minocycline; PBO, placebo; SMD, standardized mean difference.

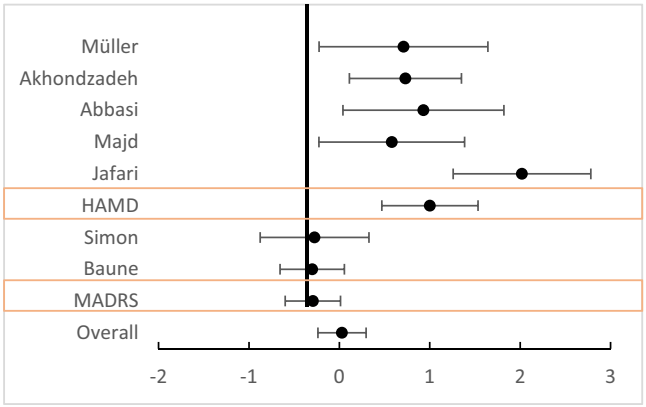

Figure 2 Forest plot of standardised mean differences and 95% confidence intervals for randomized controlled trials evaluating the efficacy of celecoxib in depression treatment using HAMD and MADRS outcome scales.
Abbreviations: HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; CXB, celecoxib; PBO, placebo; SMD, standardized mean difference.

Disclosure

The authors report no conflicts of interest in this communication.

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