Trial failures of anti-inflammatory drugs in depression

In the largest randomised controlled trial of its kind, published by Muhammad Husain and colleagues in *The Lancet Psychiatry*,[1] two drugs with anti-inflammatory properties failed to separate from placebo in reducing depressive symptom scores in a sample of patients with bipolar depression. The pressing question is: why did this trial fail? If left unanswered, an entire strategy for treating depression could be jeopardised. Among the many considerations are the design of the trial and the drugs used.

Testing anti-inflammatory drugs to treat depression should at the very least target patients with increased inflammation. Although inflammatory status was a post-hoc consideration in this study, there is no a priori reason to believe that an anti-inflammatory drug would have a clinical effect in patients without substantial inflammation. Indeed, data suggest that the opposite might be true.[2,3] Less than a third of patients with depression have increased inflammation, considerably limiting the likelihood of a successful trial if only a fraction of potential participants qualifies as targets for the treatment.[4] It should therefore be no surprise that if a heterogeneous group of patients with depression is treated, any given anti-inflammatory drug will have no or limited effects. This result has been the case with virtually every trial to date, leaving researchers bereft of the pivotal data required to interpret results. A match–mismatch trial design is preferred, with patients stratified by inflammatory status at baseline and then randomly assigned to receive an anti-inflammatory drug or not.[2] With such a design, only those with increased inflammation would be expected to respond.

A second design consideration is the outcome variable. Given the selective effects of inflammation on brain circuits and symptoms,[2] a more nuanced approach to choosing relevant outcomes is required. For example, studies using potent cytokine antagonists in patients with depression found preferential effects on anhedonia, and yet no specific measures of anhedonia were included in the trial.[3,5] Thus, without embracing the literature on the effects of inflammation on the brain, a trial with overall depressive symptoms as the primary outcome is a lost opportunity and a likely failure.

Another major consideration is drug selection. Both of the anti-inflammatory drugs used in this trial (and most other treatment trials) have a multitude of off-target effects,[2] which, when coupled with the trial design issue already mentioned, defy determination of whether any response or lack thereof is related to the effects of the drug on inflammation. Of note, neither drug was found to decrease peripheral inflammatory markers, which does not instill confidence.[1] Using drugs that have clear effects on peripheral or potentially central inflammatory endpoints, or both, might be a more useful standard upon which research can build.

Without innovative trial designs, biologically based clinical outcomes, and more selective drugs, researchers fail to take advantage of the unique opportunities of the increasing knowledge base regarding the role of inflammation in depression. Psychiatric research should be held to a higher standard, and trials should be tailored to pathophysiology, using sophisticated match–mismatch designs and outcomes relevant to inflammation's effects on the brain, and using drugs that show target engagement in the CNS or peripheral blood. With this strategy, failure to inform is not an option.

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*Andrew H Miller, Carmine M Pariante
amill02@emory.edu

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA (AHM); and Centre for Affective Disorders, Stress, Psychiatry and Immunology Laboratory and Section of Perinatal Psychiatry, National Institute for Health Research, and Maudsley Biomedical Research Centre, King's College London, London, UK (CMP)

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Authors' reply

We thank Andrew Miller and Carmine Pariante for continuing the discussion of our study, published in *The Lancet Psychiatry*.[1] They propose that our negative study might have detected an antidepressant benefit of the two anti-inflammatory drugs (minocycline and celecoxib) if we had selected a group with evidence of inflammation, used more nuanced outcome measures, and tested other drugs.

We accept that anti-inflammatory trials in depression should aim to show efficacy in people with inflammation and not in people without. The problem is that evidence of inflammation is ill-defined and so far confined to minor increases in C-reactive protein (CRP), with cut-offs