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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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

varying between 1 mg/L in 60% and 5 mg/L in 30% of patients with depression.[2] No validated stratification algorithm incorporates the many other peripheral markers of inflammation, and none are convincingly predictive of neuroinflammation. Recent trials of anti-inflammatory drugs that stratified participants at baseline according to biochemical (CRP) and phenotypic (obesity) evidence of inflammation failed to show superiority of two drugs over placebo in patients with both unipolar and bipolar depression.[3,4] If our sample had an appreciable number of patients with a responsive immune pathogenesis, this was not reflected in greater variance in outcome measures in the actively treated groups.

Regarding outcome, improvement in overall depressive symptoms must surely remain the gold standard in randomised controlled trials of pharmacological and psychosocial interventions in mood disorders. However, it is entirely appropriate to use exploratory and experimental measures to probe mechanisms such as anhedonia, but Miller and Pariante leave these measures undefined. There are several questionnaire and performance measures of anhedonia, which itself has several dissociable components. Using multiple nuanced outcome measures dilutes statistical power. Miller and Pariante cite two studies showing anti-inflammatory effects on anhedonia, but both are negative for depression, and one assessed anhedonia by a single item (work and interests) of the Hamilton Depression scale, which seems like a flimsy proof of concept for anhedonia as the primary outcome in an anti-inflammatory trial in depression.

The suggestion that minocycline and celecoxib have too many off-target effects to interpret a negative effect has no basis. The unspecified off-target actions do not prevent the undoubted efficacy these drugs in treating inflammatory disorders such as rheumatoid arthritis. The same actions in bipolar depression did not affect depressive symptoms. Furthermore, we reported that minocycline was clearly an effective adjunct in non-bipolar treatment-resistant depression,[5] a subtype convincingly associated with raised CRP.[6] In keeping with the current study, the effective anti-inflammatory cytokine inhibitor, infliximab, did not affect depression in bipolar patients selected for having CRP of at least 5 mg/L.[3] It seems a reasonable inference that in bipolar disorder, inflammation is not a pervasive mechanism of depression.

We fully agree that stratification, use of target-specific drugs, and innovative trial designs are important for progress in developing the immune strategy for treating depression. For this to happen, an urgent need exists for the definition and validation of immune subtypes of depression and for feasible biomarkers for neuroinflammation.

MIH is a principal investigator for a trial sponsored by COMPASS Pathways Limited, for which he receives salary support. BD has worked as scientific consultant to Autifony in the past 3 years and has share options in P1vtal.com. IBC has given lectures and advice to Eli Lilly, Bristol-Myers Squibb, Lundbeck, AstraZeneca, and Janssen Pharmaceuticals, for which he or his employing institution have been reimbursed. BHM currently receives research support from Brain Canada, the Canadian Institutes of Health Research, the UK Centre for Addiction and Mental Health Foundation (CAMH), the Patient-Centered Outcomes Research Institute, the US National Institutes of Health (NIH), Capital Solution Design (software used in a study funded by CAMH Foundation), and HAPPYneuron (software used in a study founded by Brain Canada). Within the past 5 years, BHM has also received research support (medications for NIH-funded clinical trials) from Bristol-Myers Squibb, Eli Lilly, and Pfizer, and he directly own stocks of General Electric (less than US$ 5000). AHY has been commissioned to provide lectures and advice to all major pharmaceutical companies with drugs used in affective and related disorders and has undertaken investigator-initiated studies funded by AstraZeneca, Eli Lilly, Lundbeck, and Wyeth.

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Cannabidiol for cannabis use disorder: too high hopes?

In *The Lancet Psychiatry,* Tom Freeman and colleagues[1] reported results from a first of its kind, phase 2a randomised trial on the effect of different doses of cannabidiol for the pharmacological treatment of cannabis use disorder. The trial appears to be well designed, and the authors concluded that both 400 mg and 800 mg cannabidiol were safe and more efficacious than placebo at reducing cannabis use.

As in previous cannabidiol trials targeting psychosis,[2] the safety profile was satisfactory, with no serious adverse events reported and only a small number of reported sleep-related problems in the cannabidiol 400 mg group. No sleep-related problems were reported in the cannabidiol