We agree that having a reference drug in clinical trials is desirable. However, our colleagues acknowledge the practical difficulties and the many design issues with active comparator trials. In addition, for bipolar depression there is no established effective reference therapy.[2] Bipolar depression is typically resistant to treatment, which was one of the rationales for our study.

We observed a marked decline in Hamilton Depression Rating Scale (HAMD) scores overall, from 24·5–25·2 to 11·3–12·8 with a mean final score of 12 (SD 7).[3] However, many participants had final scores greater than 18 (which was the inclusion severity criterion) and 186 (70%) of 266 did not remit.[3] Remission rates were sufficiently higher in those receiving celecoxib to just miss Bonferroni-corrected significance.[3] This finding might indeed indicate that inflammatory factors play a weak role in the overall group or stronger effects in subgroups. Nevertheless, our results suggest that there was room for improvement that the treatments did not fill.

The idea that bipolar depression is too heterogeneous for a one-target therapy to show benefit seems an unwarranted counsel of despair. Single action therapies do work for heterogeneous disorders such as major depression,[4] suggesting common pathways. Furthermore, inflammation is not a unitary target; it is multidimensional to the point of defying agreed definition. Minocycline and celecoxib have different cellular and molecular targets. We tested them alone and in combination. Our design was a multitargeted attempt to block the inflammatory pathways implicated in mood disorders.

Bipolar depression does not respond well to SSRIs, which suggests that it has an underlying unity and a pathogenesis distinct from unipolar depression. Although anti-inflammatory drugs show promise in treating unipolar depression, it should not surprise or disappoint us that they might not in bipolar depression. In our data, participants treated with minocycline ended with marginally higher scores on the 17-item and 24-item HAMD scales than those not so exposed; this result was nominally statistically significant on two-tailed tests, in one case surviving Bonferroni correction. This finding is unimportant clinically and possibly due to chance. It could be a signal that microglial activation, if it occurs in bipolar disorder, is protective rather than pathogenic. This notion is increasingly recognised in neurodegenerative disorders and different from proposed inflammatory mechanisms of unipolar depression.[5] In conclusion, we believe the overall negative effect of minocycline, which opposed our a priori hypothesis, is a true negative result and not due to the methodological issues raised by Berk and colleagues.

We agree that our study "might not be the last word on the potential role of anti-inflammatory drugs in the treatment of bipolar depression". We simply argue that further trials like ours are not justified until we have stronger evidence for immune activation in bipolar depression and a set of specific and sensitive biomarkers for detecting it beyond a plasma cytokine level.

MIH reports being the principal investigator for a trial sponsored by COMPASS Pathways, for which he receives salary support. BD reports scientific consultancy to Autifony in the last 3 years and has share options in P1vtal.com. IBC reports giving lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca, and Janssen Pharmaceuticals, for which he or his employing institution have been reimbursed. MIH and IBC were previously trustees of the Pakistan Institute of Learning and Living. BHM reports research support from Brain Canada, the Canadian Institutes of Health Research, the CAMH Foundation, the Patient-Centered Outcomes Research Institute, the US National Institute 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), reports research support in the past 5 years (medications for NIH-funded clinical trials) from Bristol-Myers, Eli Lilly, and Pfizer, outside the submitted work, and directly owns stocks of General Electric (less than US$5000). AHY reports giving lectures and advice to all major pharmaceutical companies with drugs used in affective and related disorders, and reports investigator-initiated studies funded by Astra Zeneca, Eli Lilly, Lundbeck, and Wyeth.

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## The 341 737 ways of qualifying for the melancholic specifier

There is considerable symptom heterogeneity in major depressive disorder. Here, we show that melancholia, which is a specifier for major depressive disorder in the DSM-5 and is meant to identify a more homogeneous subgrouping of individuals, features over ten times

more heterogeneity than does major depressive disorder.

There are over 280 ways to measure depression, which capture considerably different symptom content, with seven common scales measuring over 50 disparate symptoms. The DSM-5 criteria for major depressive disorder require a person to have at least five of nine symptoms, at least one of which has to be either sad mood or anhedonia. All symptom criteria, apart from sad mood, are compounds that contain "or" in the description, such as loss of interest or pleasure, allowing for qualitatively different ways to qualify for the same criterion. If the subsymptoms are ignored, 227 unique ways exist to qualify for major depressive disorder (appendix). Considering important qualitative differences for six of the compounds, such as loss of interest or pleasure and hypersomnia or insomnia, leads to 10 377 unique symptom profiles. Although this exercise is only mathematical, empirical work has shown that many of these profiles can be seen in patients with depression. For instance, we identified 1030 unique profiles in 3703 patients with depression from the STAR*D study,[1] 83·9% (864 of 1030) of which were reported in five or fewer participants.

See Online for appendix

To tackle this widely known heterogeneity in the presentation of major depressive disorder, clinical researchers use subtypes or specifiers. Although these two terms are often used interchangeably, the DSM-5 differentiates between subtypes (which are mutually exclusive) and specifiers (which are non-exclusive). In the past century, dozens of depression subtypes have been proposed and discarded, such as endogenous depression, introjective depression, and anaclitic depression.[2] The DSM-5 contains five symptom specifiers for depression: psychotic, catatonic, atypical, anxious, and melancholic. Of these specifiers, melancholia is one of the oldest, linked to conceptualisations of depression from centuries ago, and is the focus of this letter.

Depression with melancholic features was first operationally defined in the DSM-III, and critically discussed at the time of its implementation in the 1980s. Nowadays, the debate about the validity of melancholia is ongoing and unresolved.[3] The DSM-5 operationalises melancholia by eight symptom criteria that overlap in part with major depressive disorder, and additional symptoms, such as lack of reactivity to stimuli that are usually pleasurable, profound despair, and waking up early in the morning. A diagnosis of melancholia requires the presence of major depressive disorder, anhedonia or absence of mood reactivity, and at least three of the criteria for the melancholia specifier.

Although the DSM-5 states that specifiers can help to identify homogeneous subgroupings of individuals, this seems highly unlikely. Similar to major depressive disorder, we calculated all of the unique symptom profiles for melancholia, without and with splitting two qualitatively different compounds into subsymptoms. This calculation leads to between 10 999 and 341 737 unique profiles; over an order of magnitude more profiles than we identified for major depressive disorder (227–10 377 profiles). Given that major depressive disorder is required to qualify for the melancholic specifier, the increased heterogeneity of melancholia is not surprising mathematically, but contrasts with the intuitions that are often held about the term specifier.

Evidence for the validity or clinical use of depression specifiers is weak.[2,3] Although studies initially reported that specific antidepressants are more efficacious than others for treating particular specifiers studies done in larger samples in the past decade did not replicate these findings.[4,5] These more recent results are not surprising if specifiers are more heterogeneous than the higher-order category of major depressive disorder, which is already highly heterogenous. Further, specifiers are common, often overlap, and might not be temporally stable, raising other problems of validity.[3,5]

The pronounced heterogeneity of melancholia as a specifier in the DSM-5 challenges the idea that melancholia identifies a more homogeneous group of patients. This finding calls for investigations that extend our analyses to other depression specifiers, especially those that add a polythetic symptom set, and also to specifiers of other mental disorders. Further, these results call for research into whether the large number of unique profiles created by the specifier for melancholia can be seen in patients. Given that unique profiles are observed in patients with major depressive disorder,[1] it is not unlikely that this is true for specifiers.

We declare no competing interests.

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