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.

*Muhammed Ishrat Husain, Bill Deakin, Imran B Chaudhry, Benoit H Mulsant, Allan H Young
ishrat.husain@camh.ca

Centre for Addiction and Mental Health, Toronto, ON M6J 1H4, Canada (MIH, BHM); Department of Psychiatry, University of Toronto, Toronto, ON, Canada (MIH, BHM); Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK (BD, IBC); Department of Psychiatry, Dow University of Health Sciences, Karachi, Pakistan (IBC); Ziauddin University Hospital, Karachi, Pakistan (IBC); and Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (AHY)

1 Husain MI, Chaudhry IB, Khoso AB, et al. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. *Lancet Psychiatry* 2020; **7:** 515–27.
2 Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016; **16:** 22–34.
3 McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial. *JAMA Psychiatry* 2019; **76:** 783–90.
4 Salvadore G, Nash A, Bleys C, et al. A double-blind, placebo-controlled, multicenter study of sirukumab as adjunctive treatment to a monoaminergic antidepressant in adults with major depressive disorder. American College of Neuropsychopharmacology Annual Meeting; Hollywood, FL, USA; December 2018.
5 Husain MI, Chaudhry IB, Husain N, et al. Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial. *J Psychopharmacol* 2017; **31:** 1166–75.
6 Chamberlain SR, Cavanagh J, De Boer P, et al. Treatment-resistant depression and peripheral C-reactive protein. *Br J Psychiatry* 2019; **214:** 11–19.

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

800 mg group suggesting that this was probably a spurious finding. However, in terms of efficacy, care should be taken to not overinterpret the benefits of cannabidiol based on this trial. Naturally, being a phase 2a trial, proving efficacy was not the main aim of the trial. Furthermore, compared with the placebo group, the increase in abstinence from cannabis was 0·48 days per week (95% interval estimate 0·15 to 0·82) in the cannabidiol 400 mg group and 0·27 days per week (–0·09 to 0·64) in the cannabidiol 800 mg group. These figures reflect that all groups, including the placebo, abstained from cannabis for between 4 and 5 days in the fourth week of treatment. In other words, participants in all groups still used cannabis, on average, between 2 and 3 days per week. Although this is an improvement over using cannabis 5 or 6 days per week, reported at baseline, the difference between the cannabidiol and placebo (close to half a day increase in abstinence per week, at best) seems of questionable clinical relevance, and we would argue that this is hardly the key to remission from cannabis use disorder. For example, for patients with alcohol use disorder, an intervention that made a person with alcohol use disorder continue to consume alcohol 2 or 3 days per week would be viewed skeptically. The same pessimistic stance should be taken for cannabis use disorder. For many years, research on cannabis use disorder has taken an approach of harm reduction, in which a reduction in cannabis use is seen as an improvement; this is evident because almost all randomised trials use frequency or quantity of cannabis use as the primary outcome rather than absolute rates of complete abstinence.[3] Although this approach might hold true for frequent users without addiction-like problems, it is less clear why cannabis use reduction should be seen as adequate in people with actual cannabis use disorder. As evident in the appendix of the Article, participants receiving cannabidiol 400 mg and cannabidiol 800 mg had nominally higher urinary 11-nor-9-carboxy-δ-9-tetrahydrocannabinol:creatinine ratio at the last follow-up visit than they did at baseline.[1] The interval estimates were wide (701·05 [167·96–1234·14] in the 400 mg group and 364·70 [158·73–570·66] in the 800 mg group compared with 228·54 [87·04–370·04] in the placebo group), so this finding could be coincidental; however, it could also be an indicator that the initial reduction (without cessation) of cannabis use is not maintained and that it could also even be harmful, leading to an eventual increase in use of cannabis. It might also be interesting to consider a treatment approach of initial combined treatment with cannabidiol and (low concentration) tetrahydrocannabinol, to alleviate initial withdrawal symptoms, and subsequently switching treatment to pure cannabidiol. A parallel concept using nabiximols (a combination compound containing both tetrahydrocannabinol and cannabidiol) for treatment of cannabis dependence was found to decrease days of cannabis use by 18·6 days (compared with placebo) during a 12-week randomised trial by Lintzeris and colleagues.[4]

Fundamentally, partial abstinence as a short-term outcome might hold promise for a better long-term outcome. It could still be the case that a gradual decrease in cannabis use, rather than acute withdrawal, is acceptable as a first step towards eventual complete abstinence. This approach would then indicate a need for longer study durations than the 4-week period in the trial by Freeman and colleagues,[1] a point that the authors acknowledge.

We believe that a change in paradigm is needed for research in treatment of cannabis use disorder, away from harm reduction, focusing on complete abstinence from cannabis. Although the study by Freeman and colleagues[1] is a phase 2a trial and thus not designed to establish efficacy, the trial does not raise much hope that full abstinence will be fully attainable by cannabidiol alone; however, more research is needed before such a conclusion can be reached. This study is very important as the first step to explore how cannabidiol might have a place in treatment of cannabis related disorders. Much more research is needed concerning optimal dosing and timing of treatment with cannabidiol while also considering that the efficacy of cannabidiol compared with placebo might depend on the specific individual (eg, degree of motivation to change, duration of cannabis use disorder, and psychiatric comorbidity).

LB is the principle investigator of a randomised trial investigating cannabidiol for treatment of patients with dual diagnosis. LB is part of a research application for funding of a separate cannabidiol trial in which Tom P Freeman is also involved (this study has not yet been funded). CH and CMP declare no competing interests.

*Carsten Hjorthøj,
Christine Merrild Posselt,
Lone Baandrup
carsten.hjorthoej@regionh.dk

Copenhagen Research Center for Mental Health – CORE, Mental Health Center Copenhagen, Copenhagen University Hospital, DK-2900 Hellerup, Denmark (CH, CMP); Department of Public Health, Section of Epidemiology (CH), Department of Clinical Medicine (LB), University of Copenhagen, Copenhagen, Denmark; and Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark (LB)

1 Freeman TP, Hindocha C, Baio G, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry* 2020; published online July 28. https://doi.org/10.1016/S2215-0366(20)30290-X.

2 Davies C, Bhattacharyya S. Cannabidiol as a potential treatment for psychosis. *Ther Adv Psychopharmacol* 2019; **9:** 204512531988191.

3 Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder. *Cochrane Database Syst Rev* 2016; published online May 5. https://doi.org/10.1002/14651858.CD005336.pub4.

4 Lintzeris N, Bhardwaj A, Mills L, et al. Nabiximols for the treatment of cannabis dependence. *JAMA Intern Med* 2019; published online July 15. https://doi.org/10.1001/jamainternmed.2019.1993.