Treatment of major depression

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Here are some suggestions for using gene editing while safeguarding ethical and social considerations. First, more robust ethical guidelines and frameworks should be created. Ethical guidelines need to be reviewed and strengthened internationally to make them transparent and inclusive, involving stakeholders such as ethicists, scientists, and patient groups.

Second, public engagement and open dialogue should be encouraged. Public awareness on advances in gene editing technology and their implications is crucial. Scientists, policy makers, and other stakeholders should prioritise building trust and involving the public in discussions on gene editing's ethics and social implications.

Third, a global regulatory body should be established. The absence of policy alignment between countries raises the possibility of scientists exporting their research to evade constraints established in their home jurisdictions. A UN-based global regulatory body can allow conditional gene editing use worldwide, ensuring safe and ethical conduct while identifying potential consequences.

And fourth, new international collaborations should be developed. Collaborations can promote responsible development through joint research, sharing best practices, and promoting international ethical standards.

By incorporating these suggestions, we can ensure that the use of gene editing is grounded in international ethical standards. Although personalised medicine is becoming a reality, we must not overlook the importance of addressing the ethical challenges.

We declare no competing interests.

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2 Lanphier E, Urnov F, Haecker SE, Werner M, Smolenski J. Don't edit the human germ line. *Nature* 2015; **519:** 410–11.
3 The Lancet. Human genome editing: ensuring responsible research. *Lancet* 2023; **401:** 877.
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Treatments for major depression

Here we raise several concerns regarding the Review by Steven Marwaha and colleagues.[1] First, the concept of treatment-resistant depression does not have reliable criteria for research and is conceptually empty. The key question remains whether the disorder is resistant to treatment, or whether treatments are less effective. For example, an individual participant level of analysis of clinical trial data revealed small average differences between antidepressants and placebo.[2]

Second, regarding emerging treatments, the US Food and Drug Administration even decreased the bar for evidence, granting approval for esketamine and brexanolone via expedited approval pathways with the vague designation of breakthrough therapy. For both approvals, there was scarce evidence of the benefits outweighing the harms, and many open questions.[3] Wisely, brexanolone is not approved in Europe and the National Institute for Health and Care Excellence did not recommend esketamine.

Third, the phrase "evidence exists"[1] used in table 1 of the Review appears overly positive and can obfuscate questionable evidence. For example, there are documented concerns about the internal validity of the entire body of evidence of repetitive transcranial magnetic stimulation.[4] For deep brain stimulation, the largest randomised trial to date, stopped for futility, was not cited.[5] As narrative reviews generally reach more positive conclusions compared with systematic reviews, emergent treatments for depression should have been reviewed systematically and rigorously, preferably by authors free of considerable financial conflicts of interest.

In our opinion, novel treatments should exhibit a net positive benefit to harm ratio at high evidentiary standards before raising the hopes of patients and clinicians.

We declare no competing interests.

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1 Marwaha S, Palmer E, Suppes T, Cons E, Young AH, Upthegrove R. Novel and emerging treatments for major depression. *Lancet* 2022; **401:** 141–53.
2 Stone MB, Yaseen ZS, Miller BJ, Richardville K, Kalaria SN, Kirsch I. Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis. *BMJ* 2022; **378:** e067606.
3 Cristea IA, Naudet F. US Food and Drug Administration approval of esketamine and brexanolone. *Lancet Psychiatry* 2019; **6:** 975–77.
4 Brini S, Brudasca NI, Hodkinson A, et al. Efficacy and safety of transcranial magnetic stimulation for treating major depressive disorders: an umbrella review and re-analysis of published meta-analyses of randomised-controlled trials. *Clin Psychol Rev* 2022; **100:** 102236.
5 Holtzheimer PE, Husain MM, Lisanby SH, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry* 2017; **4:** 839–49.

Steven Marwaha and colleagues[1] wrote an intriguing Review about new treatments for major depression. My concern is with regard to figure 2 of the Review, which shows the location of the effects of new treatments for depression. The figure shows that psilocybin affected seven locations (two locations of the default mode network [DMN], three of the salience network [SN], and two of the