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## Treatments for major depression

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

Second, regarding emerging treatments, the 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.<sup>3</sup> 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”<sup>1</sup> used in table 1 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.<sup>4</sup> For deep brain stimulation, the largest randomised trial to-date, stopped for futility, was not cited.<sup>5</sup> 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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