

Are emerging treatments for major depression déjà vu all over again?

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Here we raise several concerns regarding the review entitled “Novel and emerging treatments for major depression”.(1)

First, the concept of treatment-resistant depression (TRD) lacks reliable criteria for research and is conceptually empty. The key question remains is the disorder resistant to treatment, or are treatments poorly effective? For example, a recent individual participant level analysis of clinical trial data revealed small average differences between antidepressants and placebo (2).

Second, regarding “emerging” treatments, the Food and Drug Administration’s (FDA) even decreased the bar for evidence, granting approval for esketamine and brexanolone through expedited approval pathways with the vague designation of “breakthrough therapy”. For both approvals there were scarce evidence of benefits outweighing harms, and many open questions. (3) Wisely, brexanolone is not approved in Europe and NICE did not recommend esketamine.

Third, the phrase “evidence exists” 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 rTMS (4). For DBS, the largest randomised trial to-date, stopped for futility, is not cited (5). Because narrative reviews generally reach more positive conclusions compared to systematic reviews (6) emergent treatments for depression should have been reviewed systematically and rigorously, preferably by authors free of significant financial conflicts of interest.

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

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