Antidepressant-placebo differences: is the glass half full or half empty?

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Khan and Brown's work (1) on public domain data from the archives of the U.S. Food and Drug Administration (FDA) emphasizes that drug-placebo differences in recent antidepressant trials are smaller than in early investigations, and draws a number of conclusions about the nature of clinical depression and optimal trial design. Several relevant issues in regards to this and related work on drug-placebo differences in psychiatry research may be worth emphasizing.

First, it is important for psychiatry to steer an even course between the polar positions of scientism and scepticism. Mental disorders such as depression are not analogous to squares; they are not natural kinds that can simply be defined using necessary and sufficient criteria (2,3; see also 4 in this issue of the journal). At the same time, mental disorders are not social constructions that are solely determined by socio-political considerations, and that therefore differ wholly from time to time and place to place. While efforts such as the Research Domain Criteria (RDoC), which aim to ground psychiatric constructs in translational neuroscience, may help lead to advances in psychiatric nosology and clinical trials over the long term (5), iterative improvements of diagnostic criteria and guidelines will anchor clinical practice and interventional research for now and for the foreseeable future (6).

Second, it is relevant to note that psychiatry's approach to mental disorders has a great deal in common with the rest of medicine's approach to physical disorders. The rest of medicine accepts that many conditions are best conceptualized as syndromes (7). Arguably, psychiatry has led the way in terms of providing valid, reliable and useful approaches to the diagnosis of medical conditions where simple biomarkers are not available or helpful (8). While the introduction of paradigm-shifting innovations and personalized medicine initiatives in clinical trials methodology for interventional research in psychiatry may occur over time, in the shorter term we can more certainly expect iterative improvements (perhaps including ideas emphasized by Khan and Brown, such as limiting the number of sites and treatment arms) to FDA and European Medicines Agency (EMA) guidelines for undertaking pivotal clinical trials.

Third, it is crucial to emphasize that a broad range of causal mechanisms are likely involved in the pathogenesis and treatment of mental disorders such as depression (9). Not surprisingly, any specific pharmacological agent, acting on only a limited subset of such mechanisms, may have a relatively low effect size, particularly when inclusion criteria lead to investigation of a heterogeneous phenotype.

Antidepressant effect sizes may, however, be higher for some narrower phenotypes (e.g., melancholic depression) that are often excluded from clinical trials (e.g., due to characteristic suicidal ideation). Such effect sizes may also differ in the U.S. and Europe, for a range of reasons (10). Furthermore, effect sizes for psychiatric treatments are at least as high as those in the rest of medicine (11,12).

Steering a course between scientism and scepticism also means finding a balance between over-optimism and over-pessimism with regards to psychiatry in general and antidepressants in particular. We need to acknowledge the enormous advances made in psychopharmacological research over the past several decades, while also emphasizing that there remain significant needs and opportunities for better understanding the relevant proximal and distal psychobiology of mental disorders, for better implementing and scaling-up available treatments, and for more efficacious and effective drugs (13). The level of liquid in our glass is arguably at 50%, and we need to deal with this reality accordingly.

Steering a course between scientism and scepticism may also impact our perspective on the placebo response. The reliance of modern clinical research on randomized placebo-controlled trials has led to an ever growing database demonstrating that placebo is a remarkably powerful intervention for a range of psychiatric and medical conditions, including milder cases of depression (14,15). This should not be cause for embarrassment or despair for psychiatry, but rather an impetus for research on the underlying psychobiology of the placebo response, and on how to better harness such effects in clinical practice (16). Further advances in this direction would arguably help ensure that our glass is more than half-full.

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