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The Meaning and Influence of Time-Related Dropout Dynamics in Antidepressant studies - Reassessing Current Approaches

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1. Text

There is an ongoing debate on the efficacy of antidepressants, fueling research that could have a significant impact on clinical practice. A recent meta-analysis on, as of yet, the largest corpus of antidepressant studies data came out suggesting much needed reference points to be used in informing stakeholders [1]. Despite the suggestion that the issue of clinical equipoise might finally be resolved, yet another intensification of the continuing debate on issues of clinical versus statistical significance, overall effectiveness, and cost-effectiveness of antidepressants ensued. The most important conclusion of this work, that antidepressants are more efficacious than placebo in adults with major depressive disorders, although backed by seemingly sound methodology, requires a more cautious approach considering significantly lower response rates to antidepressants in the placebo-controlled compared to head-to-head studies [1]. The authors of this synthesis of available evidence explain the issue through possible influence of comparatively earlier active-group dropout in placebo-controlled studies, with participants dropping out early arguably having poorer responses, resulting in underestimation of the antidepressants' true efficacy. This effect is mitigated by utilising the last observation carried forward (LOCF) analysis [1].

Subsequent analysis on the same dataset showed that the probability of receiving placebo was the most significant response and dropout rates predictor - the response rate was lower and all-cause dropout rate was higher for the same antidepressant in placebo-controlled studies [2]. In addition to reverse expectation (expectation of being assigned to placebo group), it was again argued that applying LOCF analysis might produce results "biased downwards", with the "underestimation of the absolute response to active drugs in placebo-controlled studies" [2]. These interpretations suggest that the probability of receiving placebo is inversely correlated to the magnitude of antidepressant response, which is known from previous studies, such as the one by Papakostas and Fava [3]. In addition, it is also mediated by time-related dropout dynamics. From available data, however, one cannot tell whether, and which, active- or placebo group participants are more prone

to early dropout (all antidepressants have similar probabilities of all-cause dropouts, similar or lower than in placebo group) [1,2,3].

These time-related dynamics, together with data on exact time points at which significant differences between placebo and active group emerge, could be decisive in formulating definitive explanations. Given the lack of such information, it remains unclear if these series of events lead to underestimation or overestimation of antidepressants' true efficacy, underestimation of placebo efficacy, or simply underestimation of influence of any other (un)observed factor. Prior analysis looking into this specific issue did not find evidence that differential dropouts could explain the difference in response rates between these different study types [3,4], while more recent evidence suggests that the consequences of differential dropouts could actually move the argument in the opposite direction, showing that participants who drop out during non-inferiority multi-arm antidepressant studies were significantly less depressed than those in any of treatment groups [5]. On the other hand, one could argue that more severely ill patients are less likely to accept the possibility of being randomized to placebo and more likely to accept participation in non-inferiority trials, where they would be sure to be assigned to an active treatment regardless of randomization. Recent studies even question historically well-established beliefs about significant time gap between initiation and the onset of effect of antidepressants (it seems that significant difference between drug and placebo usually occurs in 4th week), and that response to placebo is characterized by early improvement [6-8].

In other words, we know that participants during placebo-controlled studies tend to drop out more often, and that response to antidepressant is lower, but that still leaves us no closer to the explanation of why such an effect occurs, and what are the consequences. Differential dropouts could be influenced by many factors. On the study-participants side, differential dropouts could be influenced by experiencing side effects (or nocebo effect) or (lack of) improvement due to any other specific or unspecific reasons (e.g. different socio-demographic factors or clinical characteristics) [2,5,6,7-10]. With regards to study-specific variables, results could be influenced

by the heterogeneity of study participants, different strategies and/or inconsistencies during recruitment process, studies duration, number of sites, dosing and assessment protocols, blinding and randomization limitations, outcome definitions etc [2,5,7,9,10]. Analysis, interpretation and reporting of the results are additional factors, as in the case of previously discussed studies (with rigorous sensitivity analysis applied [1]) with regard to the widespread use of the LOCF for imputing missing data [10].

The LOCF, as single-imputation method, should be used in carefully selected instances, on a dataset where missing values are missing (completely) at random – regardless of any observed or (unobserved) factors [6,10]. Applied to the dataset where missing values are not missing at random, LOCF produces a fundamentally unpredictable bias that is relatively more prone to overestimate treatment effects, and to underestimate the influence of standard errors [7,10]. Interrelationship between these factors (and the list is more illustrative than exhaustive) creates such an extremely complex and dynamic matrix that one could question if the basic premise of rigorous and reproducible clinical experimental situation in this particular field is even plausible (if aims remain primarily explanatory in the terms of detecting true specific antidepressants efficacy).

Finally, dropouts in antidepressant studies are influenced by many different factors, most of which are still unknown, and as such cannot be controlled. An effort should be made to capture all possible factors that may contribute to dropouts (and therefore response) in a given field, where issues with adherence are omnipresent [5,9]. In other words, dropout is pragmatically important outcome in its own right, and should be systematically assessed, analysed, and interpreted. Importantly, as dropouts (as missing values) are quite certainly following a non-random pattern, more appropriate methods of imputing missing data (or at least of weighting possible biases introduced by the widespread use of LOCF), such as multiple imputation or mixed-effect model repeated measure, need to be systematically applied in order to grasp such a complex missing pattern [5,7,10]. Open-data initiatives could yield positive changes (within the limits of its own practical and ethical shortcoming), as it could provide much needed individual studies' participants

data that could contribute to our understanding and dealing with complex issues at hand. Such approaches require wider scale efforts from all interested stakeholders, as they strive for inevitable cultural and paradigmatic shift, one that is in line with recent re-emphasis on scientific reproducibility, rigor and transparency.

2. Statements

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