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Letter to Editor Open Access

On Defining Valid Outcomes for Interventions in Depressive Syndromes

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Description

The theoretical review published on May's number of Depression and Anxiety by Cuijpers et al. [1] presents how effect sizes of symptom severity scores alone may not be equated to clinically relevant outcomes. As traditionally used in clinical trials for depression, often an effect size of 0.5 is considered as large enough to be meaningful. This is an arbitrarily defined statistical construct that accounts for the magnitude of the difference in symptom severity between two groups, in half a standard deviation of the total rating scale score. The authors argue that change in amount of symptoms does not equate to meaningful clinical impact unless this is perceived as such by the patient. They suggest calculating clinically meaningful effect sizes by calculating the size effect that was equivalent to a self-reported "minimally important difference" for a certain condition, in this case depression. This article brings up the issue of both validity of the outcome, as well as meaningful effect size in clinical trials. Yet, several considerations further impact clinical outcome validity—first, deciding upon what quantifies "minimal important difference" when treating depressive syndromes, and deciding of what target, i.e. severity of symptoms or their impact on functioning as perceived by the patient.

As a principle, the definition of an outcome should be based on the definition of the problem, so let's consider a couple of ideas about the nature of depression as an entity that requires clinical intervention. Depressive syndromes are for the most part a phenomenological expression, rendering reliable and measurable objective data or defined pathophysiology for diagnosis or treatment challenging. In the lack of these, the definition of the object of intervention is phenomenological and not quantitative. The phenomena that lead to a diagnosis are symptoms that are otherwise in a continuum with normal human behavior and emotions, instead of being discrete entities [2-5]. Because of this "continuum" symptoms may be considered clinically meaningful only when they impact functioning. Therefore while symptoms are what provide the phenomenological definition, impact on functioning is what ultimately determines the presence of the syndrome. This goes along with a patient's perspective of recovering psychosocial adjustment and what is most often considered as an improvement of their condition [6].

This is being caught up by mounting research [7], including the review by Cuijpers, [1] which emphasizes the relevance of functioning as an object of outcome for interventions for depressive syndromes. There are several practical arguments to use functioning outcomes instead of symptom severity scores as primary outcomes. Per definition, they are of clinical significance, as they account for the experienced limitations in personal functioning which are caused by symptoms. They also better capture the impact of subsyndromal symptoms. These are of clinical and prognostic significance, less robustly captured by symptom severity scales alone, and are of major significance to define remission [4,5]. From a broader perspective, not only human suffering, but also the societal and economical impact of depression ultimately accounts for impact on socioeconomic adjustment, making impairment a better outcome on this regard. Also, these constructs can be used to compare cost effectiveness of different interventions [8]. Despite the fact that they do not account for the phenomenological presentation, they reflect its impact which is ultimately what makes it "clinically meaningful".

Coming to the second question, how much of a difference would be clinically meaningful, it is important to distinguish between response and remission. Response is conceptually a significant difference from baseline that does not necessarily account for the resolution of the condition, whereas remission accounts for the resolution of it. This can be easily conceptualized using measures of impairment as primary outcomes, in a way that is easy to use and clinically meaningful. For example, by using SF-12, a self-rated measure of the impact of symptoms in perceived health, response could be in theory conceptualized as an effect size reflecting significant difference from the mean score associated to depression in certain population for a specific patient. At the same time, remission could be conceptualized as a score not significantly different from the score of the general population the patient can be compared with. In spite of this, as long as there are not reliable biomarkers, defining outcome will be imperfect. Using measures of impairment, such as quality of life, offers several advantages, including its easy use and clinical significance and in our opinion should be more often used both in clinical trials as well as in clinical practice as outcomes for interventions on depression.

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