Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTERS TO THE EDITOR

Trials for depressive disorder in adolescents: the emperor's new clothes

Mew et al must be commended for investigating a most basic issue in this age of hype. Their finding, 19 different instruments for assessing depression severity among 32 trials in adolescents, is depressing [1]. However, their pledge for a ''standard to enable reproducibility, comparison, and synthesis'' deserved scrutiny.

The clinical relevance is a mandatory prerequisite [2]. The statistical significance of a 1.5- to 2-point decrease in scores from scales that are frankly inadequate to assess well-being and functional outcomes (only 1 of 17 item in the Hamilton Depression Rating Scale and no items in the Montgomery-Åsberg Depression Rating Scale measure well-being) should not enduringly fool clinicians. Moreover, sexual function, a critical issue in adolescents, is also overlooked despite impaired by antidepressants. Last, withdrawal syndrome (too well documented in adults, but lately acknowledged) is never assessed in trials.

Certainly, heterogeneity of end points, among other flaws, precludes synthesis of trials. However, are syntheses needed when a trial uses the best available comparator, not a placebo, assesses clinically relevant outcomes in large series of real-life patients with adequate follow-up and without conflict of interest. This is possible: for example, FOCUS (3 thousands of patients, 103 UK hospitals, 6-12 months of follow-up) failed to evidence benefit of fluoxetine after acute stroke [3]. FOCUS should definitely end the flow of reviews or meta-analyses of a series of poor-quality studies, which began in 2011 with FLAME (3-month follow-up, 118 patients, coordinated by the 4th French university hospital), which unduly promoted fluoxetine. The PubMed search ''Antidepressant[title] metaanalysis[title]'' hits 190 publications.

I am afraid the number of large double-blind randomized clinical trials using an active comparator and assessing relevant outcomes over the long term in the real-life setting may be counted on a fitter worker's hands.

The heterogeneity in the outcomes used for adolescent depression trials is one among many pitfalls illustrating the poor quality of clinical research. In 2013, the European Medicines Agency issued a guideline for the investigation of medicinal products in the treatment of depression but the U.S. Food and Drug Administration's one remains a draft [4,5]. For outcomes, they rely on existing scales, overlooking quality of life. Only, the European Agency cited social functioning but only among secondary end points. The Patient-Centered Outcomes Research Institute, a United States Government−funded research institute created in 2010, should begin by the beginning: developing standards for judging the course of diseases.

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Response to "Trials for depressive disorder in adolescents: the emperor's new clothes," a letter to the editor by Alain Braillon, MD, PhD

Dr. Braillon raises a number of important points in response to our review of outcomes measured in adolescent major depressive disorder (aMDD) clinical trials [1]. These points are not only relevant to the field of psychiatry but bear on the design and analysis of all trial outcomes and on systematic reviews and meta-analyses of small trials. Ultimately, this discussion raises the following question: what

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is the use of a trial if the measured outcomes are not meaningful to patients and if the results cannot be incorporated in evidence syntheses?

To Dr. Braillon's first point, we agree that well-defined and clinically relevant trial outcomes are essential to overcome deficiencies of past research. We recently discussed key issues to consider when selecting, measuring, and reporting outcomes when designing or reviewing pediatric mental health trials [2]. Our call for a standard to enable trial reproducibility, comparison, and synthesis (i.e., the development of a core outcome set; COS) for aMDD [1] and other areas of mental health research [3] is related to the need to establish which outcomes are essential and important to measure [2,4]. Recent efforts in adult MDD have identified outcomes important to patients, families, and health care professionals—many of which have been rarely measured [5]. Outcome selection driven by end users of trial results is an important avenue to reduce research waste [6,7]. In the development of an upcoming aMDD COS, end users' voices will be front and center [4].

Second, Dr. Braillon highlights the importance of defining and achieving clinically important differences. A statistically significant difference does not necessarily translate to improved health or lead to changed practice or policy decisions. Although defining and justifying the minimal clinically important difference or change is commonly recommended for clinical trial protocols and reports [8], this remains a rarity [9,10], including for aMDD trials [11]. Reporting such information, however, is key to research transparency and interpretation of trial results. There is a new dawn: the DELTA^2 guidelines offer strong guidance that can address this gap [12].

Third, we agree that large, high-quality aMDD trials measuring meaningful outcomes are possible and should be performed. The development and implementation of a COS for aMDD will help ensure that results from such large seminal trials are measuring the ''right'' outcomes in the ''right'' way, assuring their validity and relevance. The reality remains that locally conducted trials will still occur, and meta-analyses will remain an important driver of clinical decision-making. Prospective meta-analyses could be used to harmonize such trials to leverage data across trials to answer clinically relevant questions in a timely fashion [13], as recently purported for the pooling of patient data across COVID-19 trials [14]. This approach has been successful in other areas of pediatric research [15,16]. Pragmatic trials that implement a mental health COS also promise to deliver large, useable data sets.

Finally, the noted lack of guidance from regulators on which outcomes should be measured is well known. However, who should decide what should be measured? Although regulators and funders undoubtedly play an important role, we believe that it should be patients and their care providers that drive the standards for relevant, valid, and feasible outcomes to measure in trials.

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