

What is treatment-resistant depression? New report calls for clearer definition to inform research, improve treatment

December 15 2021



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A group of mental health experts from research, industry, regulatory bodies and with lived experience have proposed new agreed criteria to

define the type of depression that current medications and therapies cannot treat effectively. The report aims to provide consistent definitions for future research, and especially for designing clinical trials for new medications, with the aim of helping to develop more tailored and effective treatments for people experiencing this difficult condition.

Published in *Molecular Psychiatry*, the report used a well-known method to gain consensus, the Delphi Method, which collected and summarised the views of over 60 experts in the field of [depression](#). The report was led by researchers from the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) King's College London and National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre.

Treatment-resistant depression (TRD) affects up to 30 percent of adults with [major depressive disorder](#), which is a clinical condition characterised by persistent feelings of sadness and loss of interest experienced by around 230 million people worldwide.

The term TRD is used to describe those people who have not responded to 'adequate' antidepressant treatments, but there is a lack of consensus around the concept and what is understood by 'adequate' treatments.

The authors found that there is variation around how TRD is defined, and that only about a third of studies in TRD enrol participants who met the most common definition of having experienced at least two failures with antidepressant approaches. In addition, only one in five studies enrol participants who met the additional criteria of adequate dose and duration of medications, according to the report. This questions the applicability of the results from research to the real-world and potentially hinders progress in the development of novel treatments.

First author Dr. Luca Sforzini from the Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London said: "So

far there has been confusion about what is meant by [treatment-resistant depression](#) in research, practice and regulation, and the lack of a shared understanding is creating a barrier to effectively assessing current and future treatments. To address this, the report convened a range of experts to provide an agreed definition that we hope can support and accelerate much-needed progress in this field and enable the development of effective new approaches to [treatment](#), eventually helping people with depression."

The report brought together a group of international experts including those with lived experience, clinicians, academics, researchers, employees of pharmaceutical companies and regulatory bodies representatives. Using a Delphi-method-based consensus approach, the report formulated agreed definitions of TRD and a set of recommendations on researching unmet needs and designing [clinical trials](#).

Co-authors from the European Medicines Agency, Florence Butlen-Ducuing and Andrew Thomson, said: "Many antidepressants are available but there are still patients who are responding only partially or are resistant to treatments. As Scientific Officers of the European Medicines Agency, we welcome work that can improve our understanding of treatment-resistant depression and partially responsive depression and guide better clinical trials to try and address this unmet medical need."

The report strongly recommended that a clearer definition of TRD should be adopted: this would classify people as having TRD when they experience a minimal reduction in symptoms (by 25% or less) after the use of at least two antidepressants. They also suggested making a distinction between TRD and partially responsive depression (PRD), where people with PRD show a reduction of between 25 to 50% in symptoms to at least one antidepressant. This differentiation between

these levels of treatment resistance will be useful to identify who will be appropriate for certain trials and eventually for treatments, according to the authors.

Co-author Fanni-Laura Mäntylä who has experience of living with depression said: "Personally, as a patient with a very difficult and lengthy path with the recovery from major depressive disorder, I feel a clearer definition between partially responsive depression and treatment-resistant depression would be very beneficial; as well as a more patient-centric and personalised approach to the treatment."

In the case of TRD, the study also called for greater clarity around timing, so that only those with a lack of treatment response falling within the current episode of depression are diagnosed with TRD. Alongside this, the authors agreed that the TRD definition should be as inclusive as possible in terms of other types of treatments, so that it does not exclude people who have failed psychotherapy or some brain stimulation techniques.

Lead author, Professor Carmine Pariante from the IoPPN and theme lead for affective disorders at the NIHR Maudsley Biomedical Research Centre said: "This is a very exciting time for research and practice around treatment-resistant depression, with a number of innovative new approaches on the horizon such as psychedelics, anti-inflammatory medications and brain stimulation techniques. We hope our report will pave the way for the acceptance and implementation of a standard definition to ensure these new therapies work effectively in patients who are not currently helped by available antidepressants."

The authors also discussed the assessment of depression and called for more standardisation and shared practice in this area in terms of which instruments are used to provide a diagnosis or assess change in depressive symptoms. They agreed that the collection of biological data,

such as blood samples and brain scans, should be done consistently with the aim of identifying possible markers or measures that could identify people with different forms of depression that may respond to different types of treatment.

The study is part of the European Patient-centric clinical trial platforms, Innovative Medicines Initiative (EU-PEARL, IMI), a public-private strategic partnership funded by the Innovative Medicines Initiative (IMI)-2 Joint Undertaking (grant agreement No 853966) to lead the design of master protocols for future platform trials in different diseases, including MDD.

The paper "A Delphi-method-based consensus guideline for definition of Treatment-Resistant Depression for clinical trials" was published in *Molecular Psychiatry*.

More information: Luca Sforzini et al, A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials, *Molecular Psychiatry* (2021). [DOI: 10.1038/s41380-021-01381-x](https://doi.org/10.1038/s41380-021-01381-x)

Provided by King's College London

Citation: What is treatment-resistant depression? New report calls for clearer definition to inform research, improve treatment (2021, December 15) retrieved 25 May 2024 from <https://medicalxpress.com/news/2021-12-treatment-resistant-depression-clearer-definition-treatment.html>

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