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Editorial

We all know what we mean by treatment-resistant depression – don't we?†

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Summary

Although in common use, treatment-resistant depression is unhelpful both conceptually and practically. In this issue a new term, multiple-therapy-resistant major depressive disorder, is proposed; although it may be useful in guiding treatment options for patients with persisting depression, it should not be an automatic trigger for further, more invasive treatments.

Declaration of interests

I.M.A. has been a consultant for pharmaceutical companies developing and marketing antidepressants and has been an author on publications that have used the term treatment-resistant depression.

Keywords

Antidepressants; depressive disorders; nosology; diagnosis; placebo.

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> *'It is a truth universally acknowledged that a depressed person in possession of treatment resistance, must be in want of another treatment' (with apologies to Jane Austen).*

Treatment-resistant depression (TRD) is a term that has become embedded in psychiatric terminology and practice, although two recent guidelines have moved away from its use.[1,2] In the current issue, McAllister-Williams and colleagues go a step further and propose a new term, multiple-therapy-resistant major depressive disorder (MTR-MDD).[3] Leaving aside their audacity in breaking the three-letter rule for acronyms, how useful are these two terms?

TRD seems at first sight to be a simple shorthand for someone who remains depressed despite receiving treatment. This would be unexceptional were it not for its reification and application. Difficulties rapidly become apparent when trying to define it – a serious problem given its use in research to identify a homogeneous population for investigation of aetiology or response to treatment, and clinically to guide treatment options.

The 'standard' definition of TRD, failure to respond to two antidepressants each given at an adequate dose for an adequate trial,[4] raises a series of unanswered questions. Why specifically two antidepressants? What is an adequate trial and is this the same in all circumstances? Should sequential drugs from the same and different antidepressant classes (or augmentation) be treated as equivalent? What about, and how do we incorporate, other therapies such as psychological therapies and other drug, herbal or physical therapies? How is treatment intolerance and adherence taken into account? What degree of partial response is deemed non-resistant as opposed to resistant? Should treatment be considered completely independently from history and life context (e.g. personality, comorbidity, ongoing severe life difficulties)? Does treatment non-response in past episodes of depression count? How easy is it in practise to determine the number of, and degree of response to, previous treatments?

How evidence-based is TRD?

A dichotomous approach requires an agreed boundary, but TRD definitions have ranged from non-response to one antidepressant for up to 4 weeks, to a failure to respond to multiple 'adequate' trials of different classes of antidepressants and electroconvulsive therapy (ECT).[4] Because evidence is thin, reviews of the treatment of TRD can include studies with patients that do not respond to a single antidepressant,[5] confounding attempts to investigate even standard TRD as a potentially homogenous or distinct type of depression with established resistance to treatment.[6] It has been suggested that the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study supports a threshold for TRD after two failed treatments, as this is the 'inflection point' where the magnitude of response to treatment drops considerably.[7] However this interpretation is unwarranted as the treatment history of patients at entry to STAR*D is not reported and 25% of patients had been depressed for at least 2 years, making it unlikely this was the first treatment for entered patients. In addition, moving to the next step was based on intolerance as well as non-response, with a high drop-out rate between steps making generalisation unsafe. Do staging methods avoid the problems and uncertainty of a dichotomy by describing a continuum of attempted treatments (assuming a medication history can be accurately determined)? In theory they might, but they either have to set a specific stage to distinguish between patients with and without TRD, or if they do not, then the term TRD loses specific meaning. Also in practise, staging has not clarified the situation; a systematic review identified five different systems that were not fully compatible although partly overlapping, and all of which excluded psychological treatments.[8] As a group, they had been poorly assessed for predictive value, with the best being a multi-modal assessment including depression severity and duration, suggesting that the number of failed treatments alone is not as helpful as a wider assessment in predicting outcome.

† See pp. 274–278, this issue.

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Treatment resistance or depression persistence?

Conceptually the term 'treatment resistant' implies a poor response to the active ingredient of treatment. The elephant in the room in clinical trials is that the specific active effect (i.e. not accounted for by placebo) from both antidepressants and psychological treatment is small compared with the large effect seen from the placebo itself (effect sizes: 0.2–0.3 *v.* 0.9);[9–11] the latter includes the placebo effect and natural recovery. There is a modest correlation between the response to placebo and drug in antidepressant trials (r~0.4 calculated from Kirsch *et al*.[9]), suggesting at least some shared factor but, given the relatively small specific effect of most treatments, a lower response with subsequent treatment trials is more likely to be caused by less spontaneous improvement/placebo effect than 'resistance' to the specific effect, or some combination of both. In addition, the assumption that a switch to another mechanism of action converts 'non-responders' to 'responders' predominantly by a specific treatment effect is challenged by the lack of demonstrable advantage from switching between antidepressant class compared with within class after initial poor response.[6] Consequently, it is arguably better to try and understand the nature of, and reasons for, the *persistence* of depression in an individual person (with resistance to a specific treatment effect likely to play only a small part, on average). After all, depression is a heterogenous syndromal condition for which we do not have a unifying aetiology or an established understanding of treatment mechanisms.

Multiple-therapy-resistant major depressive disorder

MTR-MDD is proposed as stage of TRD in at least moderately severe major depressive disorder that provides a threshold for when to try non-standard treatments.[3] Non-standard treatments are not defined but are implied to have at least preliminary evidence for benefit. MTR-MDD is based on expert opinion for when further standard treatments are unlikely to lead to improvement, and is explicitly not claimed to indicate a subtype of depression. A real strength in this proposal is that it outlines the range of treatments that patients should have access to, and be offered trials of, when they have depression that persists despite treatment. Inclusion of psychotherapy and ECT as standard treatments is a welcome addition and highlights shortcomings in current practice, where genuine access to these is patchy and limited. The framework of the number and types of trials of standard treatments that should be considered before turning to non-standard options is a useful consensus guide that, if followed, could avoid both under- and over-treatment. The exact tally of standard treatments that need to be tried is of course open to discussion, but this proposal fills a gap in guidelines, such as those from the National Institute of Health and Care Excellence, which start the journey with an exhaustedly researched road map only for the route to disappear after the first bend.

However, there are important concerns. Given the problems with how the term TRD is used, MTR-MDD sounds unhelpful, like a category or subtype, and could well be a hostage to fortune. Furthermore, the standard/non-standard treatment distinction adds another dichotomy that is difficult to define, consisting as it does of a composite of availability, marketing licence status and strength of evidence. There is also a real danger, given that the limits of non-standard treatment are not defined, that it could be taken as a 'Quacks' Charter' to try heroic, poorly evidenced or ill-judged treatments on the personal whim of clinicians – as the history of medicine reminds us. At the very least, further work is needed in setting the boundaries.

Conclusions

The categorical label TRD is unhelpful as it gives a false sense that we know, and agree on, what we are talking about, excludes psychological treatment and implicitly makes unwarranted assumptions about a biological 'resistance' to drug therapies not present in patients without TRD. It also tends to reinforce further management, involving trying harder with variations of the same approach. This conclusion should not be taken as implying that treatments do not work (and some such as ECT rather well), but recognises that we lack the ability to predict, on an individual basis, what works for whom, and above all whether benefit, or lack of it, is related to the 'active' biological or psychological ingredient of the treatment tried.

MTR-MDD suffers from many of the problems of TRD, and as presented, makes the questionable assumption that meeting these criteria automatically warrants instigating another treatment, and usually one of a more invasive and physical nature. However, there is a case to be made for the MTR-MDD 'threshold' to be a point to seriously reappraise whether the medical model is the correct one for this person at this time. Even if it is, serious consideration needs to be given as to whether to press on harder with trying new (including non-standard) treatments or to consolidate current treatment. Alternatives need to be considered at this stage, such as reframing the problem or taking a more supportive, rehabilitative approach. The dilemma about which approach to take, and when to not do more harm than good, faces clinicians every day. The pressure to 'do something', even if futile or potentially harmful, can be overwhelming. MTR-MDD could be a helpful (if inelegant) addition to the psychiatric lexicon if it is taken as a trigger for a genuine review as to which direction to take, rather than assuming, for reasons of pride or prejudice, that there is only one road involving further, often increasingly invasive treatments.

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