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Cognitive–behavioural toxicity? Reflections from Westminster

At our local journal club at the Gordon Hospital, Westminster, we recently read the excellent paper by Crawford *et al* on patient experience of negative effects of psychological treatments.[1] All present were first struck by the novelty of the concept of considering the side-effect profiles of psychological therapies – and then, a split second later, astonished by our own astonishment. As psychiatrists thinking about aetiology and treatment, we are fed and watered on the biopsychosocial model. We are also accustomed to sharing the potential benefits and problems associated with treatments we offer, but seemingly only in matters of medication. We are grateful to Crawford *et al* for bringing this 'blind spot' to our attention and hope their paper will help raise awareness of the simple yet fundamental observation that psychosocial interventions may also have downsides.

As the authors have acknowledged in their 'Limitations' section, their study is not without problems. First, we – like the authors – noted the low (19%) inclusion rate of participants relative to the original sample identified. There may well be significant differences between the characteristics of the 19% who did take part and the 81% who did not, creating considerable potential for bias. Second, with a view to excluding potential confounding, we would have liked to know a good deal more about the clinical details of the participants – their diagnoses and, in particular, what other treatments they may have been receiving.

In addition to these methodological observations, we were left with a sense that the practical applicability of the study's findings is significantly limited by the lack of what the authors term 'qualitative data about negative effects'. When trying to imagine ourselves drawing on the paper as part of evidence-based practice, we strongly suspected that patients would not find it helpful to be told that there is a 5.23% chance they will have 'lasting bad effects from the treatment'. We would be keen to know more about what the authors' 'ongoing analysis of in-depth interviews' has revealed in this regard.

Finally – more at the level of intrigue than critique – we were interested by two findings which appear to point in rather different directions. The first is the strikingly low rate (5.23%) of reported side-effects of therapy, with roughly 87% of respondents reporting no negative effects. Taking into account the earlier point about giving as much consideration to potential side-effects of psychological (and social!) interventions as biological ones, and considering that the efficacy of psychological therapy is, at least for some conditions, broadly similar to that of medication, the side-effect rates identified seem almost too good to be true. We wonder if this may reflect a corollary in patients of our own hitherto lack of awareness of the potential downsides of psychological treatment. On the other hand, our eyes were caught by Table 3 of the paper, which seems to indicate that receiving a large number of sessions of psychological treatment is associated with an increased rate of side-effects. Of course, it may be that the higher number of sessions is due to increased severity and complexity of cases, in which we would expect negative experiences (perhaps interpreted as side-effects) to be more frequent. However, we cannot rule out the possibility of the phenomenon of 'cognitive–behavioural toxicity', which should clearly be a focus for further consideration and research.

1 Crawford MJ, Thana L, Farquharson L, Palmer L, Hancock E, Bassett P, et al. Patient experience of negative effects of psychological treatment: results of a national survey. *Br J Psychiatry* 2016; **208**: 260–5.

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Authors' reply: We share Yates and Mengistu's surprise at how little attention has been given to negative effects of psychological treatments. Throughout medicine, patients are given information about potential for negative effects of treatments, so that they can make informed choices about them. The principle that people should be given information about risks as well as benefits holds true in other areas of life, such as choices that people make about investing their money. So it really is surprising that people can be referred to and take up offers of psychological treatment without being told about the potential risks of treatment.

In the past, paternalism meant that people could be given treatments in the belief that these were 'in the patient's best interests'. However, this approach is no longer acceptable when discussing pharmacological treatments, and we believe it is no more acceptable when discussing talking treatments.

As Yates and Mengistu point out, the low response rate to this national survey means that the data do not provide a reliable estimate of how often people experience harm from psychological treatments. Ongoing research by the study team and others will hopefully ensure that a clearer picture of the features, prevalence and risk factors for the negative effects of psychotherapy will emerge, allowing strategies to be developed that reduce these effects. Only then will patients be able to provide fully informed consent for the psychological treatments that may help their condition.

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NNT and NNH remain helpful in evidence-based medicine

We read with interest the commentary by Roose *et al* regarding number needed to treat (NNT) and the concern that this metric is difficult to interpret given the high placebo response rates observed in contemporary clinical trials.[1] The principal objection of Roose and colleagues is that 'NNTs derived from clinical trials are not directly relevant to clinical decision-making, because they are based on control conditions that do not exist in standard practice'. Although we agree that this can limit the utility of NNTs from some studies, we contend that NNTs commonly remain 'indirectly' relevant, as explained below.

Indirect comparisons of effect sizes among different medication choices can be quite helpful in ranking interventions for both

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efficacy and common tolerability challenges, provided that the studies used for these calculations are similar enough. Number needed to harm (NNH) values may be even more helpful when distinguishing among treatments that are relatively otherwise similar.[2] The NNH can be for overall tolerability (discontinuation because of an adverse effect) or the occurrence of specific adverse effects of concern for individual patients being treated (such as sedation, weight gain or akathisia). Moreover, ratios of NNH to NNT can provide overall estimates of the risk–benefit trade-offs involved. Finally, we suggest that all of the above concepts are straightforward enough for average clinicians to calculate and understand.[3,4]

1 Roose SP, Rutherford BR, Wall MM, Thase ME. Practising evidence-based medicine in an era of high placebo response: number needed to treat reconsidered. *Br J Psychiatry* 2016; **208**: 416–20.

2 Ketter TA, Miller S, Dell'Osso B, Calabrese JR, Frye MA, Citrome L. Balancing benefits and harms of treatments for acute bipolar depression. *J Affect Disord* 2014; **169**: S24–33.

3 Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract* 2013; **67**: 407–11.

4 Citrome L, Ketter TA. Teaching the philosophy and tools of evidence-based medicine: misunderstandings and solutions. *Int J Clin Pract* 2009; **63**: 353–9.

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Authors' reply: Drs Citrome and Ketter appear to appreciate the concern we raised about the limitations of applying the NNT from placebo-controlled studies to the clinical situation (where there is no placebo control condition). However, in their letter they maintain that, 'Indirect comparisons of effect sizes among different medication choices can be quite helpful in ranking interventions for both efficacy and common tolerability challenges, provided that the studies used for these calculations are similar enough'. We do not disagree; in fact, we quoted Garcia in our paper: 'to directly compare NNTs one needs to ensure that [. . .] the control or comparisons groups to which the treated group was compared were equivalent'.[1]

Our point in the paper was that insufficient attention is typically paid to the question of whether control conditions are 'similar enough', and we believe this point still holds. Although it is not clear from their letter to what type of situation Drs Citrome and Ketter refer, one is likely on firmest ground when comparing NNTs and NNHs for antidepressant medications calculated from placebo-controlled trials of similar methodology and quality. However, even in this optimal case, it has been established that placebo response can vary significantly from trial to trial, and thus the control conditions for two studies may in fact be less similar than one might suppose.[2]

Perhaps it would be less problematic to compare the NNTs and NNHs calculated from a comparator trial of two or more antidepressants, because of course in this case there is no issue about the similarity of the studies. The problem is that, to our knowledge, there has not been a consistent finding that one antidepressant has therapeutic superiority or greater tolerability compared with another. One must be careful not to use the NNT and NNH from a single study when that finding has not been replicated, especially since comparator studies are primarily industry-sponsored.

Beyond the specific case of comparing two antidepressant medications, the points made by Citrome and Keller are not relevant to the fundamental thesis of our paper that NNTs calculated from placebo-controlled trials do not inform the clinician's choice whether to prescribe or not prescribe. Additionally, our further point still stands that NNHs and NNTs cannot be applied without significant confounding to decisions of whether to prescribe medications or psychotherapy, since the control conditions for these treatments are usually radically different.

1 Garcia AM. What does ''work'' mean? Reopening the debate about clinical significance. *Clin Psychol Sci Pract* 2010; **17**: 48–51.

2 Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002; **287**: 1840–7.

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Challenges in developing feasible and cost-effective therapies for use in LMICs

Chowdhary *et al* conducted the research reported in their paper[1] under the aegis of PREMIUM (a Program for Mental Health Interventions for Under-Resourced Health systems) in India. They state the overall aim of this programme in their introduction: 'to investigate a systematic, reproducible method for developing psychological treatments that incorporate global evidence, are contextually appropriate and can be delivered by non-specialist health workers'. In this paper, the authors set out to develop an intervention to be delivered by lay health workers, with the intention of addressing the treatment gap for mental health. The elaborate methodology they adopted to develop this intervention requires a highly skilled research team such as their own. There are simpler and more economical methods for cultural adaptation of evidence-based therapies[2,3] that have been tested in similar cultures and well described. We are not clear about the rationale for their use of a complex and expensive methodology, given the aim of a 'reproducible method for developing psychological treatments'. The authors started with a pool of techniques that were considered to be useful. These techniques were mostly based on cognitive–behavioural therapy (CBT). However, based on expert advice, they adapted the manual *Behavioral Activation for Depression: A Clinician's Guide*. A massive evaluation found this intervention to be unfeasible. Therefore, they further adapted the intervention and tested it in a pilot study. The title of their paper does not reflect the fact that this was an adaptation of an existing intervention and not the development of a new intervention. They used a complex, time-consuming and resource-intensive process that is highly unlikely to be repeatable in low- and middle-income countries (LMICs).

We have adapted CBT for the local population in Pakistan and for the ethnic minority population in England.[2,3] These methods of adaptation have been described in detail and have been tested for depression[4] and schizophrenia,[3,5] and in a guided self-help format for depression.[6] The methodology evolved over the years, resulting in the development of semi-structured interviews that can be conducted by students and easily analysed using a framework analysis method.[5] This low-cost methodology is being used in China and the Middle East to adapt CBT. We hope the authors find this work useful in their future attempts to adapt therapy.

The issue of cost becomes even more important in the delivery of therapy. In our two-pronged approach, therapy in secondary care was delivered by psychology graduates (with a typical monthly salary of $200) and by carers using a culturally adapted CBT-based self-help manual developed locally. No financial help was provided to the carers. We believe it is not just the development or adaptation of an intervention that is important; it should also be deliverable by existing mechanisms. This leads to our second concern: how practical it is to create a new workforce of lay therapists in a low-income country? This lack of understanding of the ground realities has possibly resulted in minimal change