Can a ‘true’ effect be built on a ‘wrong’ model?

Thase et al use a sophisticated model to assess the ‘true’ effect of active antidepressant therapy v. placebo.1

Health authorities generally evaluate the efficacy of new medications from randomised controlled trials (RCTs) v. placebo which are well documented and rely on such a simple statistical paradigm that they can resist the major financial conflicts of interest inherent in the evaluation of pharmaceuticals. Concerning antidepressants, these studies generally identify small, average drug–placebo differences.2

Using statistical modelling, other authors have addressed the question of outcome measurement3 and found that efficacy is better understood as a large effect in a subgroup of patients. This is consistent with the common clinical viewpoint.

However, Thase et al’s model leads to a curious phenomenon: everything happens as if some patients were considered as non-benefiters, whereas their final score is markedly less than the score for patients considered as benefiters. As they state, ‘Essentially, all models are wrong, but some are useful’. Can a ‘true’ effect of active antidepressant v. placebo be built on such a ‘wrong’ model?

Surely not for a health authority. Nevertheless, it could be useful for researchers and clinicians as it generates hypotheses on the manner in which antidepressants are different from placebo. In this view, it is necessary to go further and compare the characteristics of benefiters with non-benefiters with two additional perspectives:

1 to perform RCTs in populations of benefiters in order to maximise the signal and to minimise the noise – this could help to limit the number of ‘negative studies’;

2 to use antidepressants only in this subpopulation of treatment benefiters and to propose alternatives to other patients (e.g. psychotherapy, repetitive transcranial magnetic stimulation, electroconvulsive therapy).

Finally, Thase et al’s model is based on RCTs which if applied to major depressive disorder raises fundamental questions regarding internal4 and external validity.5 Even if a ‘true’ effect of active antidepressants exists, I’m not sure that it could be derived from RCTs.


Authors’ reply: We appreciate these comments about our research and agree that it would be very important to identify, if possible, clinical, neurobiological and/or pharmacogenomic characteristics of patients with depression who are likely to benefit specifically from an antidepressant. We also understand Professor Naudet’s scepticism about whether or not more complex statistical models of data analysis can or should be used for the purposes of regulatory review of novel medications. We note that although the concept of benefiter/non-benefiter is similar to that of responder/non-responder, there are fundamental differences. Although response can be calculated for each patient (either there is at least a 50% improvement or not), the benefiter variable cannot. It is the probability of the patient being a benefiter that is estimated, based on all information available for the patient (covariates and outcome variables). For instance, a patient with a baseline Montgomery-Åsberg Depression Rating Scale1 score of 30 and a Week 8 score of 5 will have a large probability of being a benefiter, while a patient with a baseline score of 30 and a Week 8 score of 25 will have a low probability of being a benefiter. A patient with a baseline score of 30 and a Week 8 score of 15 has an equal probability of belonging to either group. Although the classification of a patient as a responder or not may seem clear cut, in practice the difference between a non-responder and a responder can be due to a 1-point difference on an assessment scale.

We also think that it is important to point out that treatment with placebo in a randomised controlled trial (RCT) is not the same as no treatment. Beyond the frequent visits and detailed assessments that are part of the study protocol, patients in RCTs must meet specific inclusion criteria, and many are excluded for safety reasons. Thus, they are not representative of the patients seen in normal clinical practice. Patients participating in a placebo-controlled RCT also know that there is a chance that they are receiving placebo, possibly reducing their likelihood of responding, and patients randomised to placebo know that there is a chance that they are receiving active treatment, possibly increasing their chances of responding.

Finally, we do believe that the fundamental finding of our paper, namely that antidepressants convey large clinical benefits for a meaningful subgroup of patients with depression participating in contemporary RCTs, is a valid (‘true’) observation and, therefore, is not dependent on the use of a particular statistical model.

Declaration of interest

F.N. was a reviewer for the first draft of Thase et al’s manuscript. The above comments were in his review but were not included in their paper.

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**Effectiveness of cost-effectiveness**

In their economic modelling, Barrett & Byford\(^1\) postulate that the intervention group will have a reoffending rate of 3% vs. 5% in the non-intervention group, but give no evidence of this being the correct figure or even the justification for this being a reasonable estimate. It is possible that the authors are assuming that the protective effects of being in detention and receiving treatment as part of the dangerous and severe personality disorder (DSPD) programme reduces the risk to the public more than being released into the community. However, this protective effect may just be down to being detained, whether receiving treatment or not. In any case, for cost-effectiveness there has to be a justification for the effectiveness figures used, and none was presented in the paper. It is clear that in the modelling the best option is to be detained in a low-cost prison and the authors should have modelled the possibility of the therapeutic part of the DSPD programme having limited effect over detention, i.e. that it is the preventative detention effect that is important not the therapeutic part. The authors provide further evidence that the best management of violent offenders is for the criminal justice system to manage risk by protecting the public by keeping dangerous offenders in prison for long periods. There does not seem to be an economic reason to place these patients on a dangerous offenders in prison for long periods. There does not seem to be an economic reason to place these patients on a

**Authors’ reply:** We are grateful for Huda’s considered comments and, in particular, for drawing our attention to an error in the published paper.\(^1\) The reoffending rates of 3% and 5% applied to the economic model (and varied in sensitivity analysis in an attempt to account for the associated uncertainty) are supported by a systematic review of the literature, which identified a number of papers where rates of serious reconviction following specialist and mainstream detention were reported. Unfortunately, the references listed in support of this assertion are incorrect. The correct references are listed below.\(^2–4\) There is a similar error in the text at the top of page 338 referring to routine sources of cost data. The correct references, which are correct in Table 1, are also listed below.\(^2–7\) We apologise for failing to spot these errors earlier.

The reoffending rates applied to the economic model do not relate to the protective effects of detention but are rates reported following release from detention. They are therefore the therapeutic effects of the dangerous and severe personality disorder (DSPD) intervention vs. no DSPD intervention. The model, in fact, takes both types of effect into consideration: the therapeutic effects via the application of probabilities of reoffending once released and the protective effects via data on the differential lengths of time the groups spent in detention.

This is equally true for the analysis reporting that better levels of cost-effectiveness are achieved if the DSPD intervention takes place in a low-cost prison, as compared with the base-case analysis which modelled DSPD services as they were actually configured at that time (based in both prisons and high secure hospitals). This analysis was not an assessment of the cost-effectiveness of detaining participants in low-cost prisons. Instead, it was an analysis that assumed that the DSPD treatment programme only took place in a prison setting, rather than a high secure hospital, and simply involved replacing the cost of those who were in reality treated in high secure hospitals with the lower cost of treating them in a prison. The probability of reoffending once released from detention was not altered, so the analysis did incorporate the therapeutic effects of the intervention, and the probability of being released into the community remained the same.

We do not agree that the results are further evidence that the best management of violent offenders is for the criminal justice system to keep offenders in prison for long periods. Our results simply suggest that the DSPD treatment programme, as it was configured at the time of the analysis, was not found to be a cost-effective alternative to the situation where the programme is not available. By supporting the control condition, the results in fact support earlier release, rather than later, as the evidence suggests that those in the DSPD intervention were on average detained for longer periods of time than would have been the case without the intervention. The results do, however, support Huda’s assertion that the funding allocated to the DSPD intervention could be better spent elsewhere.


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Costs and outcomes of an intervention programme for offenders with personality disorders. *BJP*, **200**, 336–341. A number of the references in this paper were incorrect. First, under Probabilities (p. 337), citation of references 9–11 should have referred to Friendship et al (2003), Marshall (1997) and Taylor (2000) respectively. The full references are as follows:


Second, under Costs and outcomes (pp. 337–338), citation of references 16–18 should have been to references 13–15. Third, under Discounting (p. 338), reference 16 should be cited in place of reference 12. Fourth, under Main findings (pp. 339–340), references 6 and 7 should be cited in place of references 5 and 6.

Methodological discrepancies in the update of a meta-analysis: author’s reply (letter). *BJP*, **200**, 429–430. This letter was co-authored by Falk Leichsenring and Sven Rabung. Falk Leichsenring’s affiliation is as published; Sven Rabung is at the Department of Medical Psychology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, and the Department of Psychology, University of Klagenfurt, Austria.

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