BJPsych | The British Journal of Psychiatry (2012) 200, 512–514

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Contents

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 measurement[3] 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 internal[4] and external validity.[5] Even if a 'true' effect of active antidepressants exists, I'm not sure that it could be derived from RCTs.

1 Thase ME, Larsen KG, Kennedy SH. Assessing the 'true' effect of active antidepressant therapy *v.* placebo in major depressive disorder: use of a mixture model. *Br J Psychiatry* 2011; **199**: 501–7.

2 Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008; **5**: e45.

3 Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. *BMJ* 2005; **331**: 155–7.

4 Ioannidis JP. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? *Philos Ethics Humanit Med* 2008; **3**: 14.

5 Naudet F, Maria AS, Falissard B. Antidepressant response in major depressive disorder: a meta-regression comparison of randomized controlled trials and observational studies. *PLoS One* 2011; **6**: e20811.

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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doi: 10.1192/bjp.200.6.512

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 Scale[1] 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

M.E.T. is an advisor/consultant for H. Lundbeck A/S. During the past 5 years he has been advisor/consultant for, and/or received