

Ethics and science of placebo-controlled trials

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Readers of this journal might not stop to categorize their responses as communitarian rather than individualistic, but there are probably very few readers from either the clinical or basic research domains who would quibble with the ethics of using a placebo or a control in experiments. Most would regard it as unethical to do an experiment in animals or humans that was not properly controlled so that sense could be made of the findings. That said, there are problems with the current use of placebo-controlled trials in psychopharmacology.

The use of placebo in randomized-controlled trials (RCTs) was predicated in the first instance on creating a null hypothesis to test out claims that were made for treatments of uncertain efficacy. Neither placebo nor randomization is needed when a treatment unequivocally works, in the way for instance that activated charcoal does for strychnine poisoning or penicillin for bacterial endocarditis or insulin for a diabetic coma.

Those who framed the first RCTs possibly never envisaged an intermediate situation between treatments that clearly work and a debunking of claimed efficacy. However, this is the situation we face with placebo-controlled studies of modern anti-depressants, which based on data from 100 000 subjects randomized to either active treatment or placebo, show that 5 out of 10 subjects appear to respond to active treatment, while 4 out of 10 respond to placebo (Stone and Jones, 2006).

These responses furthermore were obtained on rating scale rather than real life measures. If RCTs were undertaken on treatments that work like penicillin for bacterial endocarditis, we would expect more dead bodies in the placebo arm than in the active treatment arm and once demonstrated such a finding might pose an ethical problem to further studies. In the case of the anti-depressants, however, and probably the anti-psychotics and other psychotropic agents, there are more dead bodies in the active treatment arms of trials than in the placebo arms¹ (Stone 2007).

These figures indicate that the number needed to treat (NNT) with placebo is 2.5, whereas the NNT for a specific response to drugs is 10. Given these data, and the additional risks attendant on active treatment, if clinicians were to follow the evidence, those in primary care at least would not prescribe anti-depressants as rapidly as they apparently do.

There seem to be two problems here. One is a failure of clinicians to understand what placebo-controlled trials in fact show. The second, as suggested by Kotzalidis *et al.*, is a failure of the field, when faced with data like this, to build on the science. Where are the efforts to delineate those clinical populations who are responsive to specific agents, thereby producing assay systems in which there is a more substantial difference between active agent and placebo. After something close to 1000 published trials of anti-depressants in clinical populations, a majority of which stem from companies pursuing marketing indications, as well as hundreds of healthy volunteer trials, there is little clarity on what the precise psychotropic effect of agents specific to the serotonin system might be compared with agents specific to the noradrenergic system. The fact that when a patient walks into a clinic, their physician still has no means of determining whether they might do better on a serotonergic rather than another agent signals a clear failure in the science of therapeutics.

Instead these treatments are prescribed close to indiscriminately because placebo controlled-trials have supposedly shown in a statistically significant fashion that the drugs 'work'. It is not surprising that when data from over a 100 000 patients is pooled selected rating scale findings can be shown to be statistically significant. But of the trials designed and undertaken by companies, something like 50% failed to produce a positive result. Against this background, a comment by Fisher (1935) in the *Design of Experiments* should unsettle us: 'No isolated experiment, however, significant in itself, can suffice for the experimental demonstration of any phenomenon ... In relation to the test of significance, we may say that a phenomenon is experimentally demonstrable when we know how to conduct an experiment that will rarely fail to give us a statistically significant result.'

The bottom line is that we haven't been doing good science. The studies that have been done have arguably led to a degradation of rather than an improvement in clinical practice. Recent Department of Health 2001 guidance on research, which states that research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical, seems applicable in this instance. If the science of therapeutics were demonstrably making progress, there would be much less grounds for critics to question what is being done.

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Notes

- ¹The data from the 2006 FDA antidepressant review for mortality on treatment and during the 90-day post termination of trial period, when analyzed

after stratification by trial, show a relative risk of mortality on active treatment of 1.04 (0.65, 1.67).

Competing Interests: DH has had consultancies with, been a clinical trialist for, been a speaker for, or received support to attend meetings from Astra-Zeneca, Boots/Knoll, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia and Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, and Solvay-Duphar. He has been expert witness for plaintiffs in 15 legal actions involving SSRIs and one patent case involving an anti-psychotic.

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