openmind
the mental health magazine

Published as Blinding Science in *Openmind* 2000;**102**:19

Bias in controlled trials

HOW MUCH IS THE RESPONSE TO MEDICATION DUE TO THE PLACEBO EFFECT?

The efficacy of psychotropic medication, such as antidepressants, neuroleptics and lithium, is commonly accepted as proven. The evidence for this conclusion comes from clinical trials, but bias in clinical trials is frequently underestimated. The motivation to believe in the value of medication is powerful and this piece is written to counter such wishful thinking.

Expectation that medication will produce improvement may itself produce apparent benefit. In other words, medication can have a placebo effect. Patients in clinical trials randomised to take active treatment are compared with those taking placebo medication, which is thought to be physiologically inert. Any advantage of active medication is presumed to be due to its specific effect. To prevent expectations influencing outcome the trial is conducted double-blind, which means that neither doctor nor patient are supposed to be aware of whether active or placebo medication are being taken, as tablets are made to look identical.

One of the main sources of bias in randomised clinical trials is that they are not as "double-blind" as is commonly assumed. Patients and doctors may be cued in to whether patients are taking active or placebo medication by a variety of means. In fact if treatment is clearly superior to placebo, this should be obvious to raters in the trial making it not technically blind. There is evidence even of deliberate deceit, such as trialists holding up to the light sealed envelopes which contain the coded allocation of patients, so that the allocation shows through and the concealment is therefore broken. Patients in clinical trials are naturally curious to ascertain whether they are in the active or placebo group, and may for example notice that placebo tablets they have been taking taste differently from medication to which they have previously become accustomed. Active medication may produce side effects which distinguishes it from inert medication.

These problems of unblinding may be minimised by trialists because there seems to be nothing that can be done to prevent it completely. This verdict may be true but there should then be no pretence that unbiased evaluation of treatment is being carried out. Although the apparent specific effect of treatment may not be as great as the placebo effect itself, it may merely be the wishfulfilling amplification of nonspecific effects. Using active placebos, which are active drugs without apparent specific treatment effects, generally reduces the effect size of the active treatment, maybe because patients are less likely to be unblinded in the trial because of the detection of active effects in the control drug.

On average the response to placebo in clinical trials is about 75% of that of active drug, irrespective of drug type. The response to placebo is, therefore, substantial. The remaining 25% of the drug response may be a true pharmacological effect, but the possibility that it is an enhanced placebo effect cannot be excluded. Studies where an attempt to measure unblinding has been made confirm that it does occur and significant correlations with efficacy ratings have been found.

The importance of establishing how much the response to medication is due to the placebo effect is relevant to problems in discontinuing medication. People may form attachments to their medications more because of what they mean to them than what they do. Psychiatric patients often stay on medications, maybe several at once, even though their actual benefit is questionable. Any change threatens an equilibrium related to a complex set of meanings that their medications have acquired. These issues of dependence should not be minimised, yet commonly treatment is reinforced by emphasising that antidepressants, for example, are not addictive.

Scepticism about the value of psychotropic medication may be rejected because it is regarded as undermining people's faith in their treatment. The issue is really about the scientific validity of claims for efficacy. There is more uncertainty about this issue that many seem prepared to accept.