Dissecting the therapeutic response

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The ultimate measure of success in clinical medicine is our patients' clinical improvement. Whenever the therapeutic response is convincing, all seems to be well. A favourable outcome implies that our diagnosis was correct and our treatment effective. In this article I wish to challenge this view as being simplistic, and try to dissect the factors which determine therapeutic success in various situations.

In daily practice, we regularly see patients suffering from condition x and improving after treatment y. Such observations are akin to uncontrolled studies in which a group of patients with condition x receive treatment y. If the outcome is favourable we tend to attribute this to the efficacy of the treatment. We often forget that numerous other factors may have contributed to the observed clinical improvement (table 1). Some of these factors are well known and therefore need no explanation: the natural history of the disease, regression to the mean, the therapeutic relationship, placebo effect. Other factors may be less obvious contributors to the observed therapeutic response. Some patients may have used other treatments which they fail to inform us of. If effective, these concomitant interventions will, of course, have contributed to the observed clinical outcome. Many patients try to please their doctor, particularly if he showed them kindness and willingness to help. Thus patients may say they feel better when in fact they do not, a phenomenon often called social desirability. In uncontrolled observations a therapeutic response can thus be determined by the specific effects of the therapy administered, plus a host of other factors (table 1).

Table 1

Potential non-specific contributors to an observed therapeutic effect in various study types.

Situation Contributing factor	Uncontrolled observations	CCT experimental *vs* no treatment	RCT experimental *vs* no treatment	RCT double-blind placebo-controlled
Natural history of the condition	√	f.a.f	f.a.f	f.a.f
Regression towards the mean	√	f.a.f	f.a.f	f.a.f
Therapeutic relationship	√	√	√	f.a.f
Placebo effect	√	√	√	f.a.f
Concomitant treatments	√	f.a.f[1]	f.a.f[1]	f.a.f[1]
Social desirability	√	√	√	f.a.f
Nocebo effect of non-treatment	n.a.	√	√	f.a.f
Hawthorne effect	n.a.	√	√	f.a.f
Patient preference	√	√	√	f.a.f

√ = Factor is likely to contribute to the observed therapeutic response.
n.a. = Not applicable
f.a.f = Factors accounted for (ie, factor is the same in both groups; between-group comparisons are therefore unaffected).
CCT = (Non-randomised) controlled clinical trial.
RCT = Randomised clinical trial
[1] Provided they are similar in both groups.

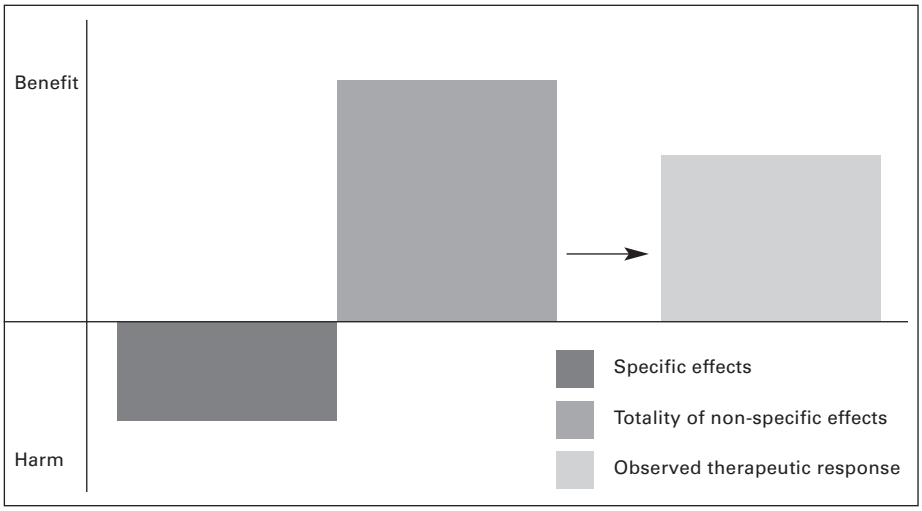

Figure 1

Schematic depiction of a positive therapeutic response after a treatment with harmful specific effects.

An example of this type of scenario is a prospective, multicentre cohort study of 3981 German and Swiss patients treated by classical homoeopathy [1]. The average effect size across different conditions was 1.6 for adults and 2.0 for children. Due to the multitude of factors which may have contributed to this result, the causality between the homoeopathic treatment and the observed effect is simply not known. Because of this multitude of factors we may perceive clinical improvements even if the treatment in itself has no specific effect whatsoever. It is even conceivable that a treatment with harmful specific effects will be followed by symptomatic improvement, if the total size of all the non-specific effects is greater than the specific effect of the treatment (fig. 1).

In a controlled clinical trial (CCT) we may compare one group of patients receiving treatment y with another receiving no treatment, or we may compare treatment y plus usual care with usual care alone. Any difference in outcome between the two groups tends to be attributed to the specific effects of the experimental treatment. This conclusion would, however, ignore the many factors that may contribute to this intergroup difference (table 1). A group receiving no treatment obviously cannot benefit from the doctor–patient relationship, or from a placebo effect, while the experimental group may profit from both. Similarly, social desirability is a possible confounder. Furthermore, patients in the untreated group or those in the usual care arm may also feel disappointed at not receiving the experimental treatment. Their disappointment may, in turn, adversely influence the clinical outcome. Thus a "nocebo effect of non-treatment" may contribute to intergroup differences in such studies. Simply being under observation may also influence patients' outcome, a phenomenon known as the Hawthorne effect. If the group allocation in such a trial is by choice, any strongly felt patient preference would exaggerate intergroup differences. Thus the results of non-randomised CCTs are influenced by a confusing variety of factors other than the specific effects of the treatment under investigation.

Randomisation may effectively eliminate the influence of patient preference on outcomes. Yet all the factors which otherwise contribute to the therapeutic response in CCTs are also relevant for randomised clinical trials (RCTs). An example of this scenario is a trial of acupuncture plus usual care versus usual care alone as a treatment for low back

pain [2]. In this RCT, 241 patients were randomised and the results showed more pain relief in the acupuncture group than in the controls. The authors conclude that "an acupuncture effect" was identified. Arguably this is not correct – the outcome could be due to a range of other effects (Table 1).

The most appropriate design for checking these factors is the placebo-controlled, double-blind RCT. But even with a trial design of this kind we should always consider possible caveats. For example, experimental treatments may generate characteristic adverse or specific effects. Such phenomena may lead to a degree of "deblinding", eg, patients guessing correctly which treatment they received. In turn, this could influence expectations and hence the placebo response. This inequality would therefore tend to exaggerate the observed therapeutic response. Examples of this scenario are trials of garlic for hypercholesterolaemia [3]. Due to the body odour caused by the regular intake of garlic in high doses, both the patient and the trialists can easily tell whether garlic or placebo has been administered. The lesson here is simple: blinding should not be taken for granted but must be controlled if we want to be sure.

Dissecting the therapeutic response in this way reminds us why observations without controls are unreliable, and highlights the multitude of factors contributing to the results of CCTs. It also shows why placebo-controlled, double-blind RCTs generate the most reliable information on the causal relationship between a specific therapeutic effect and a clinical outcome.

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