Complementary Therapies in Medicine (2013) 21, 98—101

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevierhealth.com/journals/ctim

The placebo response in clinical trials—the current state of play☆

Paul Enck*, **Sibylle Klosterhalfen**

Department of Psychosomatic Medicine, University Hospital Tübingen, Germany
Available online 18 January 2013

KEYWORDS
Randomized controlled trials;
Placebo effect;
Placebo response

Summary While randomized, placebo-controlled double-blinded trials have become the pharmacological standard over the last 60 years, the gain in knowledge of the mechanisms behind the placebo response in recent years has raised substantial concerns about the appropriateness of some of its underlying assumptions. The following questions will be addressed: Is the assumed model of drug and placebo being additive (still) valid? Does the likelihood of receiving active treatment affect the placebo response? What is the size of the placebo response in ''active comparator studies''? Minimizing the placebo response/maximizing the drug-placebo difference? How to maximize the placebo response in daily medicine? What is the placebo response with personalized medicines in the future? This and other questions require answers that can only be generated with more experimental studies on the placebo response and with thorough meta- and re-analyses of placebo responses in clinical trials.

While randomized, placebo-controlled double-blinded trials have become the pharmacological standard over the last 60 years, the gain in knowledge of the mechanisms behind the placebo response in recent years[1] has raised substantial concerns about the appropriateness of some of its underlying assumptions.[2]

A number of questions have been raised:

Is the assumed model of drug and placebo being additive (still) valid?

It is a general convention in all randomized, placebo-controlled and double-blinded trials to calculate the drug efficacy by subtracting the placebo effects (in ''efficacy'' in placebo arm) from the efficacy of the intervention in the drug arm of the study to obtain the ''true'' drug efficacy. The implicit assumption of this ''additive model''[3,4] is that in both the drug and the placebo arms the drug-unspecific responses (that include the placebo response) are equal. This model reflects a general assumption in almost all placebo-controlled drug trials that have been performed since its beginning in the mid of the last century[5–7] (Fig. 1).

Interestingly the underlying hypothesis that the placebo response is equal in size irrespective of whether an active drug or a placebo was given, has never been thoroughly tested. Some novel findings even argue against it: Petrovic et al.[8] demonstrated that separate mechanisms have to be accounted for the placebo response in an (open) drug trial

☆ Supported by a grant from Deutsche Forschungsgemeinschaft, En 50/30-1.
* Corresponding author at: Department of Internal Medicine VI: Psychosomatic Medicine and Psychotherapy, University Hospital, Frondsbergstr. 23, 72070 Tübingen, Germany.
E-mail address: paul.enck@uni-tuebingen.de (P. Enck).

0965-2299/$ — see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctim.2012.12.010

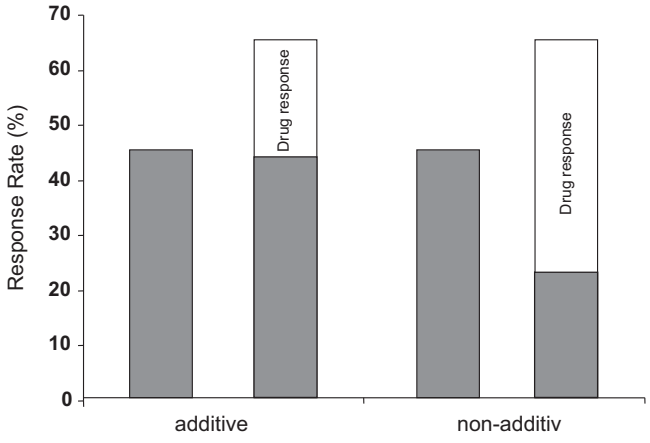

Figure 1 The assumption of the ''additive model'' according to Kirsch[4]: the size of the placebo response is assumed to be equal in the drug and in the placebo arm of trials. Alternatively, it could be smaller or greater (as indicated here) in the drug arm as compared to placebo.

(with an opioid agonist) and following application of placebo in an expectancy trial. While the drug caused greater activation than placebo in the rostral anterior cortex, placebo caused greater increase in the lateral orbitofrontal and the ventrolateral prefrontal cortex; both however, were effective in reducing experimental pain.

This can be taken as evidence that the placebo effect during open drug treatment — which is inherent to all drug applications — must be different from the placebo response during the placebo analgesia experiment, and that the placebo response during drug administration potentially ''underestimates'' the placebo response possible with expectation-induced placebo analgesia — hence argues against the additive model.[9]

Does the likelihood of receiving active treatment affect the placebo response?

First evidence for a dependency of the placebo response on the likelihood of receiving active treatment derives form a recent paper by Lidstone et al.[10] on placebo-initiated dopamine responses in Parkinson's Disease: The clinical response to varying likelihood of active treatment showed maximal response for 50% and 75% chances of receiving active treatment compared to 25% and 100%.

Some clinical data also suggests that the number of study arms in a trial, e.g. with various dosages of the drug against placebo codetermines the size of the placebo and the drug response. In two meta-analyses of depression trials[11,12] it was shown that the lower the likelihood of receiving active treatment (as compared to placebo), the lower the response to placebo and to drug. Similar findings were made for migraine[13] earlier and for schizophrenia treatment recently[14]: with trial designs that randomized 50% of patients to either drug or placebo (called 1:1 ratio trials here) the placebo response would be lower compared to trials with two or more drug arms and higher numbers of patients assigned to active treatment compared to placebo (called 2:1 or $\geq$2:1 ratio trials). Evidently, this relates only to parallel group designs and not to cross-over trials.

Interestingly most meta-analyses would ignore this and would instead process various drugs arms against the same placebo arm without adjusting for the likelihood of receiving active treatment.

What is the size of the placebo response in ''comparator'' studies?

Active comparator trials (or: comparative effectiveness research, CER) provide 100% security to receive active treatment hence they resemble the ultimate extreme to 1:1 trials. From the above discussed, one may expect a further increase of the placebo response.

In depression treatment, effective drugs are available and have been used as comparators for the test of novel compounds. Rutherford et al.[15] compared the efficacy of various antidepressants in 48 placebo-controlled studies with 9515 patients treated to the efficacy of the same drugs in 42 CER studies with 7030 patients and found on average a 15% higher response rate of the drugs in the comparator trials that they attributed to expectancy responses (patients knowing that they would receive active treatment anyway). Since the average placebo response in the placebo-controlled trials was 35%, they calculate a total of 50% placebo response in comparator trials.

In consequence, CER trials increase the placebo response without being able to control for it. Another methodological problem with CER trials is the selection of a ''fair'' and adequate comparator.

While active comparator trials may be ethically justified — no patient is left without treatment — they require more patients to be included into a drug trial than with conventional placebo controls for statistical reasons, and are therefore at conflict with the Declaration of Helsinki, according to which the minimum number of patients should be exposed to drug testing.

Minimizing the placebo response/maximizing the drug-placebo difference?

A number of drug study design features have been developed over the past decades (Table 1) to minimize the placebo effects in drug trials, and to maximize the drug-placebo difference.

Most of these have not been able to ''eliminate'' the placebo response, and have casts doubts as to whether this is a valid goal at all. The same holds true for other quality measures of drug testing for the same reason (Table 2).

Current thinking is that rather than eliminating the placebo response in drug trials, allowing a certain degree of placebo response to occur — e.g. by varying the information provided to the patient — may be a better way to control for it and to optimize drug-placebo differences.[16]