EDITORIAL

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Placebo Harm

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Rief et al.[1] reported in *Drug Safety* on adverse reaction reporting in the placebo groups of controlled clinical trials of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), and their results are fascinating and important. They had two main findings: that systematic assessment of adverse effects led to higher rates of reporting, and that the profiles of adverse effects were different in the two placebo groups, i.e. 'adverse effects patterns of the drug group are closely related to the adverse effects of the placebo group'. This finding was robust after regression analysis.

Another important observation has been made by Silberman,[2] writing in *Wired* magazine. His article is about an observation that placebos are getting more effective, and it is also an interesting review of some of the work on placebos.

There is indeed a huge literature on the placebo response (some argue that 'placebo effect' is wrong because the placebo is devoid of intrinsic activity), but less on the harmful placebo, i.e. 'nocebo', effects. Use of the term nocebo dates from Kennedy[3] in 1961, but the principle is much older, dating back to witchcraft and voodoo practices of causing harm to enemies. If those old reports are to be believed, the nocebo effect is very powerful, unto death! We certainly know that placebo effects can affect physical function, with arguable evidence for being able to alter muscle tone, blood pressure, heart rate and sensorimotor responses, and improving immune response, asthma, endurance, strength, Parkinson's disease, fever and analgesia, and probably more. Some say that the effects are short-lived, whilst others maintain longer lasting effects – up to years in one study on rheumatoid arthritis. The effects are mediated through the nervous system and there is good evidence for changes in neurotransmitter levels, induced brain function and plasma cortisol. On the other hand, there seems to be a large variation in the proportion of people who will respond to a placebo, possibly around 30% but the range is nearly 0–100%. Some say the young are better responders, others say the elderly, but many would say that it is not easy to identify responders, and certainly not across different ethnic groups.

A single placebo/nocebo (P/N) mechanism of action probably does not exist, but there is general agreement that conditioning and expectation are important factors in determining a particular response. We are not sure that even this is always so. Levine et al.[4] showed that when they told subjects that a treatment would improve motion sickness, the sham treatment was experienced as having worse effects than if they were told at the outset that the treatment would make them worse! It is also difficult to see why the colour of medications or their dosage form (which do make a difference to placebo response) could be easily ascribed to 'expectation'.

Our purpose in this editorial is not to review the literature on (P/N) response in any depth, but to consider the consequences of variability in the (P/N) response and its impact on drug safety and therapeutics.

1. Variation in Response to Placebo

Rief et al.[1] showed systematic differences in the nocebo response in two antidepressant control groups, which reflect the adverse reactions to the active drugs. They speculate that investigator

bias may lead to increased reporting of adverse effects. This could certainly lead them to expect and record adverse effects they know to be associated with the active group, perhaps paying less attention to others. Systematized methods for collection of event data would limit this effect.

A second possibility they consider is that the patients themselves may have been previously exposed to drugs of the same type as the active trial drugs; their prior knowledge would bias their expectations and reporting.

A third possibility is that information on adverse reactions in the consent form may bias reporting. This raises an interesting ethical dilemma since one clear consequence might be an underestimation of the adverse effects of the active drug, given that they may not reach a significant incidence above the control, thereby influencing any benefit-risk analysis of the drug. Does this consideration mean that patients should not be warned of possible adverse effects in a trial? It is certainly worth considering the wording and content of consent forms, and the way the information is presented.

Another point is to speculate on the effect of being told that one has a 50% chance of receiving a placebo in a clinical trial. How does that affect one's expectations? One can imagine that the overall expectations of a therapeutic effect are lowered, thereby enhancing the chances of a statistically significant positive result comparing the active group with the control group. Could such a response depend on the nature of the individual? The opposite contention was reported by Silberman[2] and has fascinating implications: more people nowadays are positively reacting to placebos. Are we actually being conditioned to expect success from drug treatments, so that we even respond more strongly and positively to placebo treatment in a controlled trial? Or is it that we respond more positively to all the care and personal attention we get in a trial, which we might think is increasingly lacking in medical care in general (and even life in general)?

The argument that the active adverse effect of the drug will always be obvious above the P/N effect is statistically unsound (a large placebo response will overshadow a small active effect), and it may also be that mechanistically the nocebo effect can either be additive/synergistic or antagonistic to the adverse effect of the drug, depending on the pathways of action involved.

2. Nocebo Response and Pharmacovigilance

We all know that not all adverse effects in case reports are due to the active substance or even the excipients. We often blame background disease or chance. We rarely discuss the nocebo effect as such. It is clear that the nocebo effect can be induced by negative expectations related to the patient's background: previous adverse reaction experiences, negative peer pressures or unsympathetic and brusque healthcare practitioners. Subtle effects of the dosage form, such as colour (change of colour if generic substitutes are dispensed), size and type of dosage form perhaps related to ease of use, and frequency or inconvenience of dosing schedules, may all have their effect on a patient's response to a drug. The patient's attitude to, and acceptance of, their diagnosis will also have an effect. One of the authors has often seen diabetic children who complain bitterly of the pain caused by insulin injection change their attitude completely once they achieve the point where their activities are more or less normal and the fears around hypoglycaemic attacks are dealt with adequately.

It is because of this that a patient-centred approach to pharmacovigilance is essential, always looking to the root cause of the patients' concerns; pharmacovigilance is not just a regulatory exercise, it is a networking exercise in which information and experience of adverse responses to drugs is shared, and it is improved by a broader consideration of case report information than just the potential of an active substance to cause an adverse drug reaction.

3. Placebos in Therapeutics

In the past, there has been considerable debate about the therapeutic use of placebos. The general view now is that it is unethical, since it involves a deception. On the other hand, homeopathy,

some traditional medicines and other 'alternative therapies' are not only commonly used but are increasingly popular in North America and Europe. They defy scientific explanation and evaluation under the scientific criteria applied to allopathic medicines.

We really should be more concerned about their effectiveness and harm, given the stringency with which we control allopathic medicines.

We are in fact bemused and hypocritical about the use of alternative remedies, and part of the underlying challenge is to understand the placebo response and its variability. If we were able to predict the placebo response for a given condition, surely it would be ethically fine to use placebos. It really does not matter if alternative therapies are placebos, it matters that patients are effectively cured or palliated. That in turn is the skill of the healthcare practitioner to use the right therapy for the job, in the right way.

Our view of alternative medicines is that they are essentially untried by the standards of placebo-controlled trials for allopathic medicines, but that does not mean they have no effect. If we give full consideration to the study of Rief et al.[1] we must also consider that we are using placebos under the false appreciation that they are an inert gold standard by which we measure our allopathic drugs. In fact they are other interventions that induce positive and negative responses in humans, just as our drugs do, though by more obscure and unevaluated mechanisms. If we continue to use placebos as standards we should understand them better.

4. Three Ways Forward for Clinical Trials

1. All clinical trials should have a quality assured, systematized method for collecting safety data.
2. Clinical trials cannot be expected to find all safety issues depending upon the nature of the trials and their power. All new products, at launch, should have a publicly available statement on the power and limitations of the clinical studies in the pre-marketing period.
3. An obvious possibility for clinical trials is to test the patients' responses to placebo before, and/or after, the controlled part of the trial. All patients would be administered placebo for a reasonable time (depending on the disease, the drug and other factors). The 'active' product would be introduced to some subjects in a double-blind fashion for a time and then perhaps be exchanged for placebo again for a further period. A simpler version would be simply placebo – active product – placebo for all subjects, but that might be subject to chronological biases. We think the main objection may be the additional time and therefore the cost involved, but a simplistic view of placebo reaction seems untenable in accurately assessing active products.

With a more nuanced appreciation of placebo/nocebo reactions and their roles in clinical trials, healthcare providers should be better able to assess adverse drug events. Assuming that an active compound does not produce a given effect simply because the rate of the effect is similar among patients on placebo is no longer a defensible stance.

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