CHAPTER 13

Placebo effects and placebo control in clinical trials

Magdalena Pilz and Johannes Pleiner

Department of Clinical Pharmacology, Vienna University School of Medicine, Vienna, Austria

The history of placebo goes back several centuries. These “dummy pills” have been used by healers and physicians worldwide, ignored by the official medical community [1]. In 1931, Amberson et al. introduced the concept of experimental randomization to medical research via a study on tuberculosis treatment. They randomized 24 tuberculosis patients into two groups, one group receiving sano-crysin for treatment, the other group distilled water. The randomization was performed by flipping a coin [2]. Substances or medical procedures should be considered within a complex psychosocial context that may influence the therapeutic outcome [3]. A placebo can be any clinical intervention including gestures, words, devices, pills and surgery. In context with surgery the term sham is sometimes used to describe such a placebo intervention [4]. To dissect this psychosocial effect and to reject the specific action of the therapy, a dummy treatment, the placebo, is given which makes the patient believe to be effectively treated. The response to this treatment, the placebo effect, is also known under such terms as expectancy effect, context effect and meaning response. The real placebo effect is a psychobiological phenomenon that can be the result of different mechanisms including the anticipation of clinical benefit and Pavlovian conditioning [3]. Various studies suggest that there are physical aspects influencing people’s perceptions e.g. the colour and size of the pills. Others report that capsules are experienced to have stronger effects than tablets. Injections trigger a stronger placebo response than oral medication and surgery elicits probably the highest rates in placebo response [4]. It has been reported that placebos may improve subjective and objective outcomes in up to 30–40% of patients with a wide range of clinical conditions, considering that the placebo effect cannot be distinguished from the natural course of the disease, regression to the mean and the effects of other factors. In general, the presence of pain and anxiety, the involvement of immunobio-

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chemical processes and the autonomic nervous system are supposed to respond expediently to placebo, whereas chronic degenerative diseases, hyperacute illnesses like heart attacks and hereditary diseases are anticipated to resist [1].

Nowadays, the gold standard in clinical trial design is the double-blind, randomized, two-armed placebo controlled study [3] but since this first placebo-controlled trial in 1931, there has been a controversy regarding the appropriate use of placebo in clinical trials, especially when patients randomly assigned to receive placebo have forgone effective treatments [5–7]. Eventually this controversy has led to the initiation of active-control trials, where a new intervention is compared to an established one.

Conceptually the randomized, controlled trial (RCT) is not a form of individualized medical therapy; it is a scientific tool for evaluating treatments in groups of research participants, with the aim of improving the care of patients in the future. From the standpoint of research logic, RCTs generally do not intend to promote the best medical interests of enrolled subjects, but may even expose them to risks that are not outweighed by benefits. It is important that patient volunteers understand that they are enrolled in a study that may produce clinical benefits, but on the other hand may fail to produce benefits or even cause medical disadvantage. Thus, clinical research involves an inherent tension between the ethical values of pursuing rigorous science and protecting participants from harm [8].

To avoid exploiting research subjects, clinical trials must satisfy several ethical requirements. Accordingly, the use of placebo in clinical trials must be evaluated in terms of the ethical principles appropriate to clinical research, which are not identical to the ethical principles of clinical practice [9]. Clinical trials are unethical if they are not designed to answer valuable scientific questions with the use of valid research methods. In addition to having scientific merit, clinical trials must present a favourable risk–benefit ratio: the risks to participants must be minimized and justifiable by the potential value of the scientific knowledge to be gained from the study and care for future patients.

1 The recent debate about research ethics in placebo controlled trials (PCTs)

To harmonize attitudes towards ethical aspects of clinical research a number of ethical codes has been established and promoted. Perhaps the best known of these is the Declaration of Helsinki (DOH). The World Medical Association (WMA) was established in 1947, after the Second World War and today is an organization of 85 national medical associations representing roughly eight million physicians. A major revision and reorganization, specifically addressing the use of placebo (Article 29), was completed in Edinburgh, Scotland, in 2000 [10]. This revision states that “The benefits, risks,