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A Clinical Study of 46 Males With Low-Back Disorders Treated with Methocarbamol

Andres Grisolia MD and J.E.M. Thomson CORR 1959;13:299–304

The double-blind, randomized control trial (in which neither the patient nor the observer knows the treatments, each of which is administered randomly) is considered the gold standard of designs to determine the results of treatment on patients. The concept of a placebo-controlled trial is not new. None other than Benjamin Franklin proposed what is considered the first placebo controlled trial in the 1780s [7], although the experiments were only single-blinded (the subject was unaware of the treatment). Mesmerism, the invention of Anton Mesmer of Austria, was based on the concept that all illness was caused by a blockage of the body's natural flow and that magnetism (which Mesmer presumed was some sort of ultrafine fluid) restored the flow and health. Mesmer distinguished mineral and animal magnetism, and suggested the latter had curative properties while the former did not. Many of those exposed to his treatments went into trance-like or even sometimes convulsive states. Mesmer was forced out of Vienna as a charlatan, but then enchanted much of Paris. In 1874, King Louis XVI commissioned the Royal Academy of Medicine and the Academy of Sciences to study the matter. The nine commissioners (including Joseph-Ignace Guillotin, who had developed a "humane" method of execution, and

Antoine Lavoisier) engaged Benjamin Franklin, who was living at the time as an ambassador of the United States to France, and one of the world's most famous scientists [3]. At Franklin's suggestion they devised an experiment in which the subject was blindfolded and unaware of whether they were exposed to any source of magnetism. The Royal Commission concluded, "...only one cause is requisite to one effect, and that since the imagination is sufficient cause, the supposition of the magnetic fluid is useless. In all of these experiments no differences were found other than those due to varying degrees of imagination" [7]. Franklin wrote to an individual seeking his opinion on the matter, "There being so many disorders which cure themselves and such a disposition in mankind to deceive themselves and one another on these occasions...That delusion may however in some cases be of use while it lasts...If these people can be persuaded to forbear their drugs in expectation of being cured...they may possibly find good effects tho' they mistake the cause" [7].

Placebo-controlled trials are commonplace in determining the effects of drugs, with many varieties of single or double-blinded trials, without or with randomization, and sometimes with crossover (in which each subject begins with one treatment, the effect determined, then another treatment

instituted and the effect again determined). However, surgical trials introduce a number of problems. First, they cannot be blinded from the surgeon (who always knows the treatment), although sometimes they can be blinded from the patient and the observer (who need not be the surgeon). Second, trials are limited to those conditions in which two or more treatments (for example, types of implants or repairs) can be introduced without the knowledge of the subject or observer, meaning, for example, the skin incision and scar must be identical in all subjects. Third, placebo-controlled trials are generally considered unethical since surgery always entails some risk and is not performed without balancing risk and benefit, and since exposing patients to risk with virtually no chance of benefit is unethical. There are examples, however, such as a well-publicized double-blinded (patient, observer) trial of knee arthroscopy for osteoarthritis, in which the treatment group had arthroscopy, débridement, and irrigation, while the control group only had the (small) skin incisions [10]. In that trial, the treatment provided no better outcome than the placebo.

Grisolia and Thomson, in 1959, reported a preliminary trial of hospitalized patients on the use of methocarbamol (Robaxin), one of the earliest "muscle relaxants" for treating

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low back pain [8]. The trial was neither randomized nor blinded: one group received the drug and the other did not (in a true placebo trial, the second group would have received an identical-appearing tablet without the active agent), but the treatments were reportedly otherwise similar. However, the diagnoses varied, as did the dosage and duration of the drug. Their data suggested wide-ranging responses to the drug without compelling differences between the two groups, although they suggested those treated with methocarbamol had a shorter hospital stay (20 days with versus 25 days without). The data were not statistically analyzed, undoubtedly an appropriate choice given their heterogeneity. The authors, considering this a preliminary trial, stated they had engaged in a double-blind study of the drug (a trial that, if ultimately completed and reported, I cannot find). The study of Grisolia and Thomson illustrates many of the problems with clinical trials and also reflect some of the standards of the time.

Internationally accepted standards [2, 5, 6, 9] are now used to design randomized trials. Perhaps most importantly are the CONSORT guidelines [1]. By today's standards such a trial would be more tightly controlled: the entry criteria would be clear, a proper power analysis would be used

to determine the number of patients needed and accounting for dropouts, patients would be randomized into treatment groups, all treatments would be standardized, validated (most likely patient-generated) outcome instruments would be used to assess patients, all assessments would be by blinded observers, and proper statistics would be used to discern any differences in outcome measures. Ironically, relatively few current orthopaedic treatments have been subjected to rigorous trials and the quality of trials is variable at best [4]. However, such trials are expensive, time-consuming, fraught with administrative difficulties (not the least of which is seeking and obtaining approval of the appropriate ethical committees), and sometimes difficult to publish, particularly when investigators find no differences in the treatments. Throughout the history of medicine, advances have been made and older treatments abandoned primarily based on empirical evidence, rather than that from well-controlled trials; unfortunately, compared to well-controlled trials, empirical evidence is a far less efficient (and sometimes misleading) way to introduce and evaluate new treatments.

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