THE USE OF PLACEBO IS ESSENTIAL IN HEADACHE TRIALS? YES

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In 1962, the Congress of the United States passed the Kefauver-Harris Amendment that mandated that manufacturers provide evidence of drug effectiveness in addition to safety in order for the Food and Drug administration (FDA) to approve the agent for a specific clinical indication. The FDA in 1970 published guidelines describing what acceptable controls in a clinical trial were. The double-blind randomized clinical trial was established as the "gold standard" for the emerging pharmaceutical industry. In 2012, the International Headache Society (IHS) Clinical Trials Committee published "guidelines for controlled trials of drugs in migraine: Third Edition. A guide for investigators". In that document, they noted placebo rates ranged from 6 to 47% in clinical trials for abortive agents with respect to migraine relief. Placebo rates in headache reduction in preventive trials ranged from 20 to 40% (or even higher). The committee recommended that in clinical trials "Drugs used for acute treatment of migraine should be compared with placebo". With respect to preventive agents, "Drugs used for migraine prophylaxis should be compared with placebo. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity (assay sensitivity) of the trial which would allow greater generalizability of study results".

In 2002, the World Medical Association Declaration of Helsinki stated that when an effective treatment for a disease exists, it was unethical to assign patients in a research study to a treatment known to be less effective. Standards for the acceptable use a placebo in clinical trials have changed over time, and (with informed consent), it is now considered acceptable to use placebos in clinical trials in which withholding the best current treatment will result in only temporary discomfort and no serious adverse effects. The IHS guidelines (noted above) state that research protocols should allow the use of rescue medication any time after the first primary efficacy time point (typically, two hours after intake of study medication). This is necessary for the evaluation of "new treatments".

Demonstration of treatment efficacy demands that the target (active) agent must be shown to be statistically significantly superior to an inert substance (placebo) not believed to be a specific therapy for the target condition. As noted above, this is the "gold standard" in clinical research. Placebo rates (and factors that influence them) become increasingly important as potential methodological manipulations (e.g., "over-powering" clinical studies) may allow small differences between groups to reach statistical significance when, in fact, such differences may be clinically meaningless. Similarly, placebo rates have been shown to vary dramatically depending upon a variety of "non-specific" treatment factors (the type of treatment, degree of invasiveness, contextual factors in the research interactions, unbalanced randomization ratios, etc).

Placebo-related variables are believed to contribute to treatment efficacy in clinical settings. While they create "noise" in the interpretation of research results, enhancing these variables is desirable in clinical settings. In sum, issues related to placebo are extremely important variables in both research and clinical and settings.