THE USE OF PLACEBO IS ESSENTIAL IN HEADACHE TRIALS

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The term "placebo" (PL) derives from Latin "I shall please". Placebos are typically defined as physiologically inactive substances that elicit a therapeutic response. In other words, placebos induce changes in symptoms or conditions, modifying the outcome (relative to what would be expected by natural history only). The antipode of the placebo effect is the nocebo effect, or the negative effects of placebo, where unpleasant symptoms (e.g. adverse events) emerge after the administration of placebo. Placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception.

Doctors and scientists have to a large extent very different "needs" regarding the placebo effect. While doctors benefit from the placebo effect (gaining additional efficacy or further increasing tolerability), scientists often see the placebo effect as a nuisance in clinical research, focusing on strategies to neutralize it, in order to properly demonstrate the benefits of active medications.

It is established that the efficacy of treatments overall, and of headache treatment specifically, is a function of basically three factors. First, headache is likely to improve because of natural history only, as well as by regression to the mean. Headache is also likely to improve because of the *Hawthorne effect,* the tendency of people to change their behavior or condition simply as a consequence of being observed or studied, which can lead to reduced pain among patients simply because they are in a clinical trial or because they want to "please" their therapist. A second component of clinical improvement is due to the placebo effect itself. Finally, there is the benefit of clinical treatment. Accordingly, clinical improvement is a summation of natural history and other factors not related to treatment, placebo response and treatment-related factors.

The effect of placebo effect in the acute treatment of migraine is enormous. In triptan clinical trials, placebo 2-hour pain-relief rates ranged from 17% - 50% (mean = 28.5% ± 8.7%). For pain free, rates ranged from 5% - 17% (6.1 ± 4.4). Adverse events after placebo varied enormously (likely reflecting methodological discrepancies), from 4.9% to 74% (23.4 ± 14.0%). Finally, rates were higher in children and adolescents, relative to adults (pain relief = 48.5%; pain free = 25.5%).

The placebo response in migraine preventive clinical trials ranges from to 14% to 50%, depending on the duration of the study and of study-design. The nocebo effect is also relevant in preventive studies.

Accordingly, placebos are an essential component in headache clinical trials:

1. In order to allow proper interpretation of clinical research. In the context of a clinical trial, no conclusive arguments can be made in the absence of placebo. The alternative, using active comparators, requires previous validation against placebo (of the comparator) and substantially increased sample size.
2. Because the placebo response varies as a function of the route of administration and level of intervention, comparisons between different formulations or interventions require specific clinical trials. Conclusions cannot be inferred based on systematic reviews or meta-analyses
3. The therapeutic effect of any intervention is the result of the placebo effect and of the efficacy of the intervention. Similarly, the tolerability of medications results from adverse events and of nocebo. Accordingly, doctors should try to maximize the placebo effect while minimizing the nocebo effect. This is of particular importance in pediatrics, since children are especially susceptible to placebos.
4. The dogmatic concept that placebo are inert substances, without biological action, should be promptly dismissed as not supported by scientific knowledge.