



## Letters to the Editor

### RE: "BIAS IN CLINICAL INTERVENTION RESEARCH"

In her *Journal* review discussing the potential biases of controlled trials, Gluud stated that "[t]he purpose of blinding is to prevent bias associated with patients' and investigators' expectations. If interventions are compared with no intervention, an identical placebo may be used. The compared interventions must be identical in taste, smell, appearance, and mode of administration. Any difference may destroy the blinding" (1, p. 496).

The last sentence of this quotation was based on three references, two of them focusing on vitamin C and common cold trials (2, 3). However, the Karlowski et al. trial (2) and the Chalmers review (3) were both shown to be erroneous a decade ago (4–6). For example, Karlowski et al. did not mention that 42 percent of the recorded common cold episodes were missing from their subgroup analysis that was the basis for their proposal that "the effects [of vitamin C] demonstrated might be explained equally well by a break in the double blind" (2, p. 1038). In the concurrent review, Karlowski et al.'s subgroup analysis led to a proposal that, in general, "the effects of ascorbic acid [vitamin C] on [common cold] symptoms are the result of the power of suggestion" (3, p. 535).

The lack of validity of Karlowski et al.'s (2) placebo explanation is important for methodological and biologic reasons. First, the Karlowski et al. trial has been extensively used as an example of "placebo effect in action"; for example, it was the only original study cited in the CONSORT statement (7) and the *Cochrane Handbook* (8). Second, Karlowski et al.'s trial and Chalmers's review (3) are the most frequent citations in medical textbooks when stating that vitamin C is ineffective against the common cold (6), whereas placebo-controlled trials have shown quite consistently that it is effective, even though the practical significance is unsettled (9).

Furthermore, Gluud (1) did not refer to a recent, large meta-analysis of trials directly comparing a placebo group with a no-treatment group, which found no difference between the groups when the outcome was binary; only in studies on pain was there a difference between the placebo and no-treatment groups (10).

Although it is reasonable to use placebo control when feasible, particularly in trials with subjective outcomes, there is no evidence of large and universal placebo effects, and there are examples of placebo-effect speculations being misused to reject findings inconsistent with authors' preconceptions (2–6).

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