

Review: Placebo is better than no treatment for subjective continuous outcomes and for treatment of pain

Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001 May 24;344:1594-602.

QUESTIONS

In patients with various clinical conditions, what is the clinical effect of placebo as a treatment for disease? Does the effect differ for subjective and objective outcomes?

DATA SOURCES

Trials published before the end of 1998 were identified by searching MEDLINE, EMBASE/Excerpta Medica, PsycLIT, Biological Abstracts, and the Cochrane Controlled Trials Register. Reference lists were reviewed, and experts were contacted.

STUDY SELECTION

Studies were selected if patients were randomly allocated to a placebo group or an untreated group. Exclusion criteria were un-concealed randomization, a sample of paid or healthy volunteers, nonblinding of assessors of objective outcomes, a > 50% dropout rate, or if the alleged placebo had a clinical effect not associated with the treatment ritual alone.

DATA EXTRACTION

The primary outcome was that defined by the trial author or, if not defined, the most clinically relevant outcome.

MAIN RESULTS

114 trials were included. The typical pharmacologic placebo was a lactose tablet, the typical physical placebo was a procedure done with a machine turned off, and the typical psychological placebo was an attention placebo (a nondirectional neutral discussion). 40 clinical conditions were investigated.

Placebo did not differ from no treatment for binary outcomes (32 trials, $n = 3795$), regardless of whether outcomes were subjective (23 trials) or objective (9 trials) (Table); significant heterogeneity existed among trials ($P = 0.003$). Placebo did not differ from no treatment in trials assessing nausea (3 trials), smoking cessation relapse (6 trials), or depression (3 trials).

Placebo was more effective than no treatment for continuous outcomes overall (82 trials, $n = 4730$; pooled standardized mean difference [SMD] -0.28 , 95% CI -0.38 to -0.19) and for subjective continuous outcomes only (53 trials, pooled SMD -0.36 , CI -0.47 to -0.25); placebo did not differ from no treatment when considering objective continuous outcomes only (29 trials) (Table). Significant heterogeneity existed among trials ($P < 0.001$), and the magnitude of placebo effect decreased

with an increasing sample size ($P = 0.05$). For trials assessing continuous outcomes, placebo was better than no treatment for pain (27 trials, pooled SMD -0.27 , CI -0.40 to -0.15) but not for obesity (5 trials), asthma (3 trials) hypertension (7 trials), insomnia (5 trials), or anxiety (6 trials).

CONCLUSIONS

Placebo is more effective than no treatment for continuous subjective outcomes and for treatment of pain. Placebo and no treatment do not differ in trials assessing objective or subjective binary outcomes or objective continuous outcomes.

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Placebo vs no treatment for various conditions

Outcomes at end of treatment	Binary outcomes Pooled relative risk (95% CI)	Continuous outcomes Pooled standardized mean difference (CI)*
Laboratory data	0.92 (0.73 to 1.17)†	0.18 (0.02 to 0.33)
Objective, without patient cooperation	0.89 (0.66 to 1.20)†	-0.25 (-0.5 to -0.01)
Objective, with patient cooperation	0.84 (0.52 to 1.36)†	-0.21 (-0.44 to 0.02)†
Subjective and observable	0.93 (0.77 to 1.11)†	-0.41 (-0.61 to -0.20)
Subjective and nonobservable	0.97 (0.89 to 1.07)†	-0.35 (-0.48 to -0.22)

*Negative values favor placebo.
†Not significant.

COMMENTARY

The meta-analysis by Hróbjartsson and Gøtzsche is controversial both theoretically and practically. Theoretical difficulties are highlighted by the fact that the authors once argued that placebo was undefinable (1) and that the placebo effect was uncontrollable (i.e., any comparison would underestimate it) (2). The sweeping nature of the conclusions in the original paper is also questionable: A meta-analytic summary is justified insofar as a more or less similar magnitude of effect can be expected across a range of patients, interventions, and outcomes for the included studies. May we expect similar effects of comparisons of placebo and no treatment for smoking, nausea, infertility, infection, or Parkinson's disease? In my opinion, the abstract above, independently prepared by the editorial office of this journal, is a better summary.

In practical terms, it seems wise to concentrate on the substantive areas in which practicing clinicians may be interested. For pain, the pooled SMD was -0.27 (95% CI -0.40 to -0.15); the point estimate suggests a small effect, but the CI is such that one cannot rule out

the possibility of a moderate effect. For other conditions, the CIs are too wide to rule out a large-to-moderate effect. For hypertension, for example, the SMD was -0.32 (CI -0.78 to 0.13). For insomnia, it was -0.26 (CI -0.66 to 0.13), and for anxiety, it was -0.06 , (CI -0.31 to 0.18).

On the basis of current knowledge, we cannot claim that we could use "placebo treatment" for depression or anxiety (3). Nor should we talk about maximizing placebo effects in treatment unless good evidence exists to show that we really can do so (4).

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References

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3. Enserink M. *Science.* 1999;284:238-40.
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