What's in Placebos: Who Knows? Analysis of Randomized, Controlled Trials

Beatrice A. Golomb, MD, PhD; Laura C. Erickson, BS; Sabrina Koperski, BS; Deanna Sack, BS; Murray Enkin, MD; and Jeremy Howick, PhD

Background: No regulations govern placebo composition. The composition of placebos can influence trial outcomes and merits reporting.

Purpose: To assess how often investigators specify the composition of placebos in randomized, placebo-controlled trials.

Data Sources: 4 English-language general and internal medicine journals with high impact factors.

Study Selection: 3 reviewers screened titles and abstracts of the journals to identify randomized, placebo-controlled trials published from January 2008 to December 2009.

Data Extraction: Reviewers independently abstracted data from the introduction and methods sections of identified articles, recording treatment type (pill, injection, or other) and whether placebo composition was stated. Discrepancies were resolved by consensus.

Data Synthesis: Most studies did not disclose the composition of the study placebo. Disclosure was less common for pills than for injections and other treatments (8.2% vs. 26.7%; $P = 0.002$).

Limitation: Journals with high impact factors may not be representative.

Conclusion: Placebos were seldom described in randomized, controlled trials of pills or capsules. Because the nature of the placebo can influence trial outcomes, placebo formulation should be disclosed in reports of placebo-controlled trials.

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For author affiliations, see end of text.

Placebo-controlled trials usually compare the average effects of one active intervention with one placebo. Adequate description of test treatments is recognized to be important (1). Control treatments for nondrug interventions, such as sham acupuncture (2), sham surgery (3) or procedures (4), and sham exercise (5), are commonly specified and sometimes evaluated for validity (6). In contrast, the importance of adequately describing drug placebos has seldom been appreciated. No substances are known to be physiologically inert, and no regulations guide placebo composition, which can influence study results (7). Such considerations attest to the need for stating the placebo composition. We evaluated how frequently placebo composition is specified in randomized, controlled trials published in journals with a high impact factor.

Methods

We developed and followed a standard protocol for conduct of searches and data abstraction.

Data Sources and Searches

We focused on the 4 English-language general and internal medicine journals with the highest impact factors for 2009, as ascertained from the ISI Web site (www.ISIknowledge.com). These journals were *New England Journal of Medicine*, *JAMA*, *The Lancet*, and *Annals of Internal Medicine*. Three independent reviewers (Ms. Erickson, Ms. Koperski, and Ms. Sack) conducted PubMed searches through EndNote XI (Thomson Reuters, Philadelphia, Pennsylvania) for each journal, identifying candidate articles by using the keywords *randomized* (any field) and *controlled* (abstract) for the specified publication years 2008 and 2009. They screened titles and abstracts of the journals to identify randomized, placebo-controlled trials published from January 2008 to December 2009. Articles were eligible if they presented original data from randomized trials in humans and used putatively nonactive controls (placebos). We did not consider studies using cluster randomization or ahead-of-print publications.

We excluded publications from the main analysis if they cited previous publications for their primary findings or study design. In this case, failure to disclose the placebo could not be determined with certainty from the accessed article.

In a secondary analysis, we retained articles that cited previous publications in the event that the reviewed article stated the placebo composition. However, because this process selectively retains articles with a previous citation that did disclose composition, it may bias the analysis toward the appearance of greater placebo disclosure.

Data Extraction

Reviewers independently abstracted data from the introduction and methods sections of eligible articles and examined the full text when necessary. They recorded the type of treatment (pill, injection, or other) and whether the placebo composition was stated. Discrepancies were resolved by consensus. Reviewers coded publications as dis-

See also:

Web-Only
Appendix Figure
Conversion of graphics into slides

closing, partially or equivocally disclosing, or failing to disclose placebo composition. For placebo injections, we coded "saline" as bearing full disclosure, including instances in which it was not directly stated whether this meant "normal saline."

Because our intention was not to single out specific journals, journals are designated as A, B, C, and D in this article.

Statistical Analysis

We used Mantel–Haenszel chi-square analysis to assess whether reporting of placebo composition differed for pills versus other treatment types. We used OpenEpi statistical software (8) for all analyses.

Role of the Funding Source

The study was funded by University of California Foundation Fund 3929—Medical Reasoning. The funding source had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation or review of the manuscript; or the decision to submit the manuscript for publication.

Results

We identified 958 unique articles by using the search protocol (486 from 2008 and 472 from 2009). Fifty-five articles that lacked placebo specification were excluded because of designation of previous results or methods papers pertaining to the study, and 736 articles did not meet other inclusion criteria. Results of the literature search are shown in the **Appendix Figure** (available at www.annals.org). Therefore, 167 studies remained eligible. Both pills and injections were used in 8 studies, and 1 study assessed both an injection and a modified treatment given by another route of administration (intranasal spray), using placebos for each route of administration. Thus, 86 studies of pills, 65 studies of injections, and 25 studies of other treatment methods (totaling 176 studies) were examined.

One study of pills, 8 studies of injections, and 7 studies of other approaches that specified the placebo composition (or procedure), either fully or partially, also cited previous reports; of these, 1, 7, and 5 respective studies had fully stated the placebo.

Table 1 shows rates of disclosure of placebo composition by treatment type (pill, injection, or other) and journal, including results for both years. Of the studies, 8.24% that used pills disclosed the placebo constituents on the basis of an analysis in which we excluded all articles that cited previous design or primary outcome studies. In contrast, 26.3% of trials that used injections and 27.8% of those evaluating other treatment approaches disclosed the placebo (chi-square, 9.59; $P = 0.002$ for pill vs. injection and other treatments combined).

Results were similar when articles that specified the placebo composition were retained, even if they cited previous studies; we found that 9.3% of studies that used pills disclosed the placebo, compared with 33.8% of studies that used injections and 40.0% that assessed other treatments (chi-square, 17.2; $P < 0.001$ for pill vs. injections and other treatments combined). Disclosure of the composition of placebo pills was closely similar for the 2 years examined.

Table 1. **Disclosure of Placebo Composition in the 4 General and Internal Medicine Journals With the Highest Impact Factors***

Journal	Placebo Composition Disclosed/Partially Disclosed/Undisclosed, *n/n/n*			
	Pill	Injection	Other	Total
Excluding articles citing a previous design or primary findings paper				
All articles, *n*	85	57	18	160
Articles by journal				
Journal A	0/0/8	0/0/1	0/0/1	0/0/10
Journal B	5/0/13	3/0/1	3/0/0	11/0/14
Journal C	0/2/35	6/1/16	1/3/2	7/6/53
Journal D	2/0/20	6/3/20	1/4/3	9/7/43
Combined	7/2/76	15/4/38	5/7/6	27/13/120
Including articles in which placebo is disclosed and that also cite a previous publication				
All articles, *n*	86	65	25	176
Articles by journal				
Journal A	0/0/8	0/0/1	1/0/1	1/0/10
Journal B	6/0/13	4/0/1	3/0/0	13/0/14
Journal C	0/2/35	7/2/16	2/5/2	9/9/53
Journal D	2/0/20	11/3/20	4/4/3	17/7/43
Combined	8/2/76	22/5/38	10/9/6	40/16/120

* Placebo disclosure vs. no disclosure or partial disclosure differed for studies involving pills (7 vs. 78) compared with studies of injections or other administration methods combined (20 vs. 55) ($P = 0.002$, Mantel–Haenszel chi-square test). When the analysis was repeated including articles that cited a previous design or primary findings paper for that study, if placebo composition was stated completely or partially, respective values were 8 vs. 78 and 32 vs. 58 ($P < 0.001$, Mantel–Haenszel chi-square test).

Discussion

Placebo ingredients were seldom disclosed in controlled trials reported recently in journals with high impact factors. Disclosure was particularly rare for pill-based placebos.

The revised CONSORT (Consolidated Standards of Reporting Trials) guidelines request disclosure of interventions with enough detail to permit replication (1). Where relevant, they recommend describing how similar the interventions are (1) in domains "such as appearance, taste, smell, and method of administration" (9). These factors affect perceived differences between the test treatment and the placebo. In contrast, there is no requirement to stipulate the composition of the putative placebo or the inactive elements of the test treatment: That is, disclosure of the actual (chemical) differences between the placebo and test drug is not required.

However, negative, positive, or same-direction effects of a placebo can result in the misleading appearance of positive, negative, or null effects of the experimental drug (7). For instance, olive oil and corn oil have been used as the placebo in trials of cholesterol-lowering drugs (7, 10, 11). This may lead to an understatement of drug benefit: The monounsaturated and polyunsaturated fatty acids of these "placebos," and their antioxidant and anti-inflammatory effects (12, 13), can reduce lipid levels and heart disease (13, 14). In one of these studies (11), the authors commented that "The lack of any overall effect in patients with myocardial infarction might be related to the unexpectedly low mortality rate in the placebo group." The possibility that the placebo composition may have influenced this "unexpectedly low mortality" was apparently not considered.

Bias favoring the active drug can also occur. In a study of megestrol acetate for anorexia associated with cancer, an unexpected benefit of megestrol over placebo in gastrointestinal symptoms was found (15). However, a lactose placebo was used: Because lactose intolerance is prevalent in cancer, promoted by both chemotherapy (16) and radiation therapy (17), adverse effects of the lactose placebo to gastrointestinal symptoms may have contributed to the appearance of benefit from the drug (15, 18).

Such studies are not atypically flawed for choosing imperfect placebos; instead, they are singularly laudable for revealing placebo constituents and allowing concerns to be aired. Bulking agents, excipients, stabilizers, flavor enhancers, dyes, and lubricants also may have effects, and empirical evidence supports occurrence of clinically relevant sequelae (19–21).

Placebos are rarely perfect: That is, they differ from the test drug only in the presence of a putative active or characteristic feature. Indeed, this ideal may be impossible to attain. If the test drug has a fishy aftertaste owing to its characteristic element, either the placebo will not do so (giving rise to limitations in the perception of the identical nature of the placebo vs. the test drug) or a new ingredient must be added to make it do so (resulting in differences beyond the characteristic or active feature in the actual composition of the placebo vs. the test drug). Or, if the test drug occupies much of the volume of its pill or capsule, something must be substituted in the placebo to occupy this volume. Perfection in the placebo is not the aim; rather, we seek to ensure that its composition is disclosed.

Our study has limitations. Findings from 2008 and 2009 may not be generalizable to other years. However, our focus on recent years ensures that findings reflect current publication practices. The journals selected may not be representative, but the presumption is that articles in journals with high impact factors are held to a higher quality standard. Moreover, the findings for these journals are important regardless of their generalizability, because these journals have high impact. Finally, our analysis does not clarify the frequency with which placebo constituents may influence internal validity, replication, or cross-trial comparisons; because the composition of placebos is seldom stated, how frequently their composition is problematic cannot be ascertained.

In conclusion, failure to describe placebo ingredients breaches basic scientific standards of rigor. Yet, researchers may choose not to disadvantage their publication prospects by declaring placebo composition when others are not doing so. Publishers may also be reluctant to disadvantage their journals by imposing a requirement that is not an industry standard. We suggest that journals with high impact factors lead by example, by implementing a reporting requirement, and that the CONSORT Group amend its guidelines in the ways suggested in **Table 2**.

Because inferences from clinical trials propagate to clinical practice, failure to report placebo composition compromises the foundation on which medical decisions are based, and on which the fate of lives may rest.

Table 2. **Suggested Modification for the Reporting of Placebo-Controlled Trials**

Article Section and Topic	Descriptor
Description of the test agent	Was the test agent or drug described in detail? If a chemical compound, were its full constituents given by weight? Was its appearance described?
Description of (placebo) control	Was the (placebo) control treatment described in detail? If a chemical compound, were its full constituents given (by weight)? Were its appearance and any differences from the test drug described (or absence of differences stipulated)? Was it stated what other factors might render the experience of the control distinctive from the test agent (or absence of other factors stipulated)?

From the University of California, San Diego, School of Medicine, San Diego, California; McMaster University, Hamilton, Ontario, Canada; and Centre for Evidence-Based Medicine, University of Oxford, Oxford, United Kingdom.

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Reproducible Research Statement: *Study protocol and data set:* Available from Dr. Golomb (e-mail, bgolomb@ucsd.edu). *Statistical code:* Available online at www.OpenEpi.com.

Requests for Single Reprints: Beatrice A. Golomb, MD, PhD, University of California, San Diego, School of Medicine, 9500 Gilman Drive, #0995, La Jolla, CA 92093-0995; e-mail, bgolomb@ucsd.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Schulz KF, Altman DG, Moher D; CONSORT Group.** CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152:726-32. [PMID: 20335313]
2. **Kaptchuk TJ, Stason WB, Davis RB, Legedza AR, Schnyer RN, Kerr CE, et al.** Sham device v inert pill: randomised controlled trial of two placebo treatments. BMJ. 2006;332:391-7. [PMID: 16452103]
3. **Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al.** A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002;347:81-8. [PMID: 12110735]
4. **Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group.** Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004;351:2805-16. [PMID: 15625332]
5. **McCann IL, Holmes DS.** Influence of aerobic exercise on depression. J Pers Soc Psychol. 1984;46:1142-7. [PMID: 6737208]
6. **Streitberger K, Kleinhenz J.** Introducing a placebo needle into acupuncture research. Lancet. 1998;352:364-5. [PMID: 9717924]
7. **Golomb BA.** Paradox of placebo effect [Letter]. Nature. 1995;375:530. [PMID: 7791863]
8. **Dean AG, Sullivan KM, Soe MM.** OpenEpi: Open Source Epidemiological Statistics for Public Health. Version 2.3 ed. Vol. 2010; 2009.
9. **Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al.** CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. [PMID: 20332511]
10. **Acheson J, Hutchinson EC.** Controlled trial of clofibrate in cerebral vascular disease. Atherosclerosis. 1972;15:177-83. [PMID: 4579955]
11. Ischaemic heart disease: a secondary prevention trial using clofibrate. Report by a research committee of the Scottish Society of Physicians. Br Med J. 1971;4:775-84. [PMID: 4943606]
12. **Cullinen K.** Olive oil in the treatment of hypercholesterolemia. Med Health R I. 2006;89:113. [PMID: 16596937]
13. **Covas MI.** Bioactive effects of olive oil phenolic compounds in humans: reduction of heart disease factors and oxidative damage. Inflammopharmacology. 2008;16:216-8. [PMID: 18815741]
14. **Fito M, Cladellas M, de la Torre R, Alcántara M, Pujadas-Bastardes M, Marrugat J, et al; members of the SOLOS Investigators.** Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. Atherosclerosis. 2005;181:149-58. [PMID: 15939067]
15. **Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM, et al.** Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. J Natl Cancer Inst. 1990;82:1127-32. [PMID: 2193166]
16. **Osterlund P, Ruotsalainen T, Peuhkuri K, Korpela R, Ollus A, Ikonen M, et al.** Lactose intolerance associated with adjuvant 5-fluorouracil-based chemotherapy for colorectal cancer. Clin Gastroenterol Hepatol. 2004;2:696-703. [PMID: 15290663]
17. **Wedlake L, Thomas K, McGough C, Andreyev HJ.** Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: An observational study. Eur J Cancer. 2008;44:2212-7. [PMID: 18760593]
18. **Golomb BA.** Doctoring the evidence: the case against lying to patients about placebos. Am J Bioeth. 2009;9:34-6. [PMID: 20013497]
19. **Golomb B.** When are medication side effects due to the nocebo phenomenon? [Letter]. JAMA. 2002;287:2502-3. [PMID: 12020325]
20. **Eccles R.** Mechanisms of the placebo effect of sweet cough syrups. Respir Physiol Neurobiol. 2006;152:340-8. [PMID: 16326149]
21. **Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM Jr.** Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161:1140-6. [PMID: 18056558]

Current Author Addresses: Dr. Golomb, Ms. Erickson, Ms. Koperski, and Ms. Sack: University of California, San Diego, School of Medicine, 9500 Gilman Drive, #0995, La Jolla, CA 92093-0995.
Dr. Enkin: 1001 Bay Street, Apt 2404, Toronto, Ontario M5S 3A6, Canada.
Dr. Howick: Centre for Evidence-Based Medicine, University of Oxford, Oxford OX3 7LF, United Kingdom.

Author Contributions: Conception and design: B.A. Golomb, J. Howick.
Analysis and interpretation of the data: B.A. Golomb, L.C. Erickson, S. Koperski.
Drafting of the article: B.A. Golomb, J. Howick.
Critical revision of the article for important intellectual content: B.A. Golomb, L.C. Erickson, S. Koperski, M. Enkin, J. Howick.
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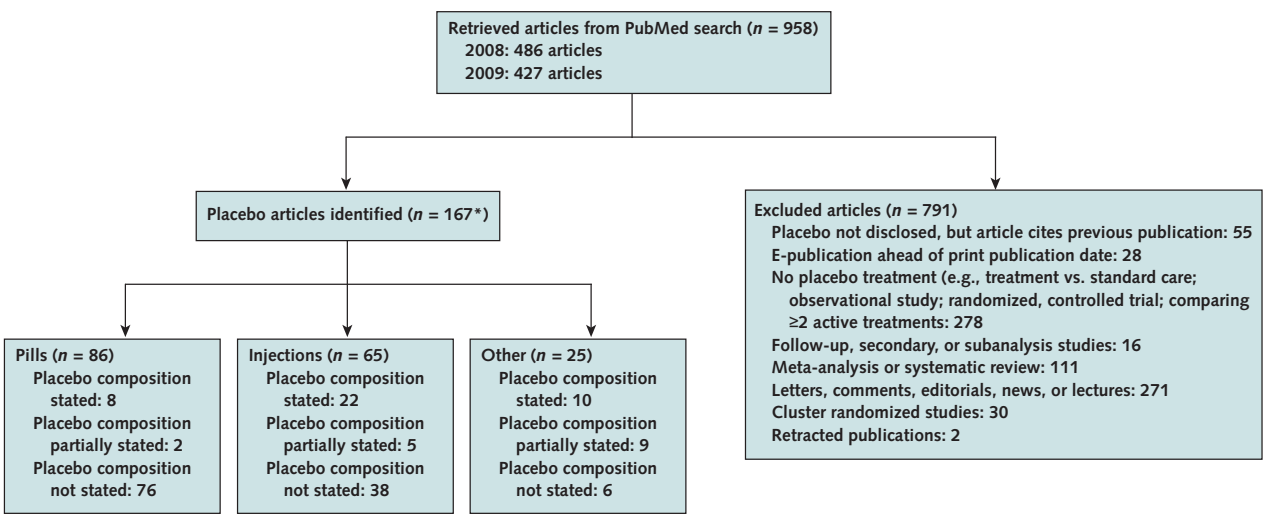
Appendix Figure. **Summary of evidence search and selection.**



* Nine articles are counted twice because they have a placebo in 2 categories.