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## Pills, Politics, and Placebos

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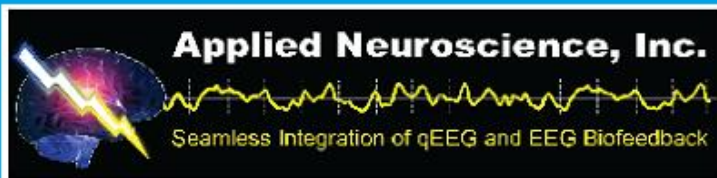
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## *CURRENT CONCEPTS IN NEUROTHErapy*

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### Pills, Politics, and Placebos

T. J. La Vaque, PhD

**ABSTRACT.** Randomized double blind placebo controlled clinical trials (RCT) are the current “gold standard” for demonstrating clinical efficacy of new drugs or therapies. It is very difficult for new therapeutic interventions to gain broad acceptance in the absence of such trials. Recent events have raised serious questions about the conditions under which placebo (sham) controls can be used. The international standards published by the World Medical Association (Declaration of Helsinki) prohibit placebo-controlled studies when known effective treatments exist. Additionally, there is new interest in identifying the mechanisms underlying the placebo response, which may challenge the “placebo” as a legitimate control condition. Both of these events should be of considerable interest to those interested in clinical psychophysiology in general and neurotherapy in particular.

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**KEYWORDS.** Ethics, placebo, RCT, Declaration of Helsinki, neurotherapy, psychophysiology, efficacy, methodology, mind-body

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The acceptance of new drugs, procedures, and therapies for the treatment of human ills is increasingly dependent upon a demonstration of efficacy through clinical trials. The use of placebo (or “sham”) controls for the study of drug and treatment efficacy has become so thoroughly established in clinical trial designs that some critics have referred to the unquestioning use of placebo controls as the “placebo orthodoxy” (Freedman, Glass, & Weijer, 1996; Freedman, Weijer, & Glass, 1996). Critics of neurotherapy point to the lack of placebo (sham) controlled studies to argue that the evidence for efficacy is poor (Arnold, 1998; Barkley, 1992). At the same time, the placebo itself is coming under increased scrutiny. There are compelling reasons that placebo controlled clinical trials should be re-examined as a standard design, most particularly in those studies examining psychophysiological therapies.

The widespread use of placebo controls in clinical trials is generally attributed to the efforts of Henry Beecher, a physician whose area of interest was the study of analgesics for pain management. It was his purpose to elevate the study of the clinical efficacy of drug therapeutics to a more objective process than was current at the time (i.e., simple professional “opinion” about what worked). At the same time, however, he remarked upon the “power” of the placebo, recognizing that at times the placebo effect “can produce gross physical change” and “objective changes in the end organ which may exceed those attributable to potent pharmacological action” (Beecher, 1955). Thus, the purpose of the double blind placebo control design was to find the “true” therapeutic effect of investigative drugs by controlling for variables such as experimenter bias, measurement error, and the influence of the placebo effect itself.

The double blind randomized placebo controlled clinical trial (RCT) design has become the gold standard for drug trials submitted to the federal Food and Drug Administration (FDA) to gain lucrative marketing approval. The RCT design also holds an important place in studies funded and conducted by the National Institutes of Health (NIH), including the recently created National Center for Complementary and Alternative Medicine (NCCAM), whose director told the NCCAM Advisory Council, “We cannot rely on anecdotes, no matter how many there are . . . randomized, double blind control studies are the gold standard” (NCCAM, 2000). Similarly, a reviewer of “alternative therapies” for the NIH Consensus Development Conference on Diagnosis and Treatment of ADHD concluded that EEG biofeedback “merits a sham-controlled randomized trial” (Arnold, 1998). However, some placebo controlled clinical trials are being criticized on both ethical and func-

tional grounds. The debate has great significance for those interested in applied psychophysiology.

### ***ETHICS AND PLACEBO***

Some medical ethicists have expressed concern about using placebo controlled clinical trials when a known effective treatment is already available, based upon the principle that it is unethical to withhold treatment from patients for experimental purposes (Lurie & Wolfe, 1997; Rothman, 2000; Rothman & Michels, 1994). The ethical problem and the source documentation have been reviewed in some detail elsewhere (Glaros, 2001; La Vaque & Rossiter, 2001a; La Vaque & Rossiter, 2001b; Striefel, 2001). Since 1964 the World Medical Association has published a document known internationally as The Declaration of Helsinki. The document codifies certain ethical principles governing biomedical practice and research and is recognized internationally. Federal agencies and private professional organizations in the United States also refer to the Declaration. In particular, the FDA participates in the publication of documents known as "ICH" documents. The International Conference on Harmonization (ICH)<sup>1</sup> is sponsored by the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the FDA Centers for Drug Evaluation and Research and Biologics Evaluation and Research, and the Pharmaceutical Research and Manufacturers of America. The FDA specifically requires that, "It should be confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki" (FDA, 1996a). ICH E6: Guidance for Industry: Good Clinical Practice (FDA, 1996b) and ICH E8: General Considerations for Clinical Trials (FDA, 1997) also specifically require adherence to the ethical principles outlined in the Declaration of Helsinki.

The principle set forth in the Declaration that has created significant controversy and political dispute is found in Section C: Additional Principles for Medical Research Combined with Medical Care, Article 29:

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1. The complete and formal name of the organization responsible for the ICH documents is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists. (WMA, 2000)

This ethical principle was brought to the fore as a result of AIDS research carried out in Third World countries. Although known AIDS treatments existed, the study used an experimental brief protocol testing a drug (zidovudine) against placebo to examine its efficacy in preventing perinatal transmission of the HIV virus to newborns. Epidemiologists Peter Lurie and Sydney Wolf objected to the studies, since it was known that zidovudine reduced HIV transmission by two thirds if administered during the last 26 weeks of pregnancy, during delivery, and to the newborn for six weeks after delivery. They argued that the study raised serious ethical concerns because the study withheld a known treatment for experimental purposes, and the design should have been an “active control” study, comparing the experimental protocol to the established protocol. The authors cited the Declaration of Helsinki principle (Lurie & Wolfe, 1997). Since that time there has been considerable debate about the use of placebo controlled designs. The debate has taken on international political importance because it has been acknowledged that such a study would never be tolerated in the western industrialized countries (McNeill, 1998). Dirceu Greco, professor of internal medicine at the Federal University of Minas Gerais, Brazil, suggested that concerns about exploitation of economically deprived countries by industrialized countries would be avoided if the new drug or treatment were tested in the country in which it is to be marketed (Ramsay, 1999; Woodman, 1999).

The FDA has been drawn into the fray. Peter Temple (Director of the Office of Drug Evaluation I and of the Office of Medical Policy) has pointed out that the use of an active control design comparing the investigational drug directly to a known treatment, lacking a placebo control, may provide no effective experimental control internal to the study, so a serious issue of *assay sensitivity* is raised (Temple, 1999; Temple & Ellenberg, 2000). Assay sensitivity refers to the ability of the study to detect any real difference between the investigational treatment and the active or placebo control. If the active control measure carries a high degree of variance, either because of measurement variance or “placebo effect,” using that active control as a standard is dangerous. It would be similar to using a standard in a biological assay which was so variable

that one could never be certain if the unknown being tested actually matched a diagnostic standard (excessive false positives and false negatives). One doubts that a couple buying an over-the-counter pregnancy test would be satisfied with a result that essentially came back “maybe yes and maybe no.” The same principle applies to standards against which new treatments are measured. If the standard treatment has a very small error of measurement and a strong treatment effect, then the assay sensitivity would be strong, and an active control treatment equivalence study (a “noninferiority study”) comparing standard and investigational treatments would be acceptable.

The statistical characteristics of an active control study, however, require a much larger “N” than does a placebo control design (Blackwelder, 1982). That being the case, Temple argues, one runs the risk of exposing a larger number of patients to an ineffective investigational treatment in an active control treatment equivalence study. From a different perspective critics argue that placebo studies are of little use clinically since they compare an investigational drug to “nothing,” and a new drug that is in every way inferior to a known drug may still get on the market. The most useful clinical information, they insist, would come from a head-to-head comparison of two drugs (Lurie, 1999). Pharmaceutical companies prefer placebo controls because they are less expensive and do not run the risks inherent in drug-to-drug comparisons of side effect frequency and severity, efficacy differences, and so forth.

Why should clinicians and investigators interested in psychophysiology in general and neurotherapy in particular be concerned about these issues? The FDA, after all, is mandated to oversee the safety and efficacy of drugs and devices and has nothing to do with procedures such as EEG biofeedback. It must be recognized that the randomized double blind placebo controlled design originally proposed by Henry Beecher for the study of pharmaceuticals is also regarded as the “gold standard” design by NIH whether one is studying drugs or procedures. The ethical issues and design issues are more readily understood when using the drug study examples as the basis of discussion, but it is important to understand that precisely the same issues often exist for the study of such diverse *procedures* as surgery (Freeman et al., 1999; Fu, 2000; Macklin, 1999), psychotherapy (Jarrett et al., 1999; Quitkin, 1999), and acupuncture (Hammerschlag, 1998). It seems that an ethical dilemma is created for those pursuing new therapies (“complementary,” “alternative,” or just “new”), since standard treatments already exist for most of the disorders of interest. If the Declaration’s prohibition of placebo controlled studies when known therapies exist is to be taken seriously, how

is one to design a study for neurotherapy and, say, ADHD, or anxiety disorders, depression, drug rehab, and so forth? It seems to be something of a “Catch-22” situation. If the studies do not contain a placebo (sham treatment), it is unlikely that the health community at large will regard the studies as legitimate demonstrations of “efficacy.” If the studies are designed with sham control or a placebo, one runs the risk of engaging in ethically questionable research.

The question is one that requires serious attention and discussion. The current status of evidence for the efficacy of neurotherapy is not very different than that which existed in the drug industry when Beecher wrote *The Powerful Placebo* (i.e., simple professional opinion about “what works”). We do not have access to protocol comparison studies. The majority of studies do not report whether the putative intervening variable (brainwave features used for the operant procedure) changes in the predicted direction and are consistent with the predicted change in the dependent variable (symptomatic change, La Vaque, 1999). We have little systematic information about the effective components of neurotherapy. A single issue of this Journal carried four reports on the treatment of attentional disorders, each using different protocols, each reporting effective remediation, and none particularly consistent with the other (Fenger, 1998; Norris, Lee, Cea, & Burshtyn, 1998; Ramos, 1998; Wadhvani, Radvanski, & Carmody, 1998). In the absence of internal experimental controls such as a sham feedback condition, the possibility that variables unrelated to the EEG operant procedures were responsible for the treatment effects cannot be ignored (Duffy, 2000).

Does that mean that placebo (sham therapy) controls are the only standard available? Not necessarily. The use of an active control design has been used in neurotherapy studies to only a limited extent (Fuchs, 1999; Rossiter & La Vaque, 1995). At a minimum, neurotherapy studies should be able to report both brainwave changes and behavioral changes co-varying as a function of the particular operant conditions used in treatment. This is no different than examining data to identify and characterize the learning curve in any operant conditioning study.

The problem of standards of evidence for efficacy is not unique to neurotherapy. The question has been examined broadly. The NIH Office of Alternative Medicine (before its status was elevated to that of a “Center” within NIH) convened a Quantitative Methods Working Group charged with the task of identifying study designs and data analysis for research in complementary and alternative medicine. The Working Group concluded that existing methodologies and data analytic techniques were adequate to the job (Levin & Glass, 1997). The ethical

problems were not addressed, but in any case recent interest in the mechanisms of the placebo effect may render their conclusion moot.

### ***FUNCTIONAL ASPECTS OF PLACEBO***

Despite the central role of the placebo or sham control designs in medical and behavioral research, relatively little is known about what “the placebo effect” actually represents on a functional level. It should be remembered that Beecher spoke of “the powerful placebo” and regarded the placebo effect not as an innocuous trick of the imagination, but as potentially very powerful, sometimes exercising greater influence over recovery from illness and “subjective symptoms” than did some drugs in use at that time. In fact, he reported that “placebo effects” were sometimes capable of *reversing* pharmacological effects. It was for that reason that he argued that the placebo condition must be used as a control condition internal to the experiment rather than relying upon external controls, such as historical data regarding the disease or disorder. He felt the placebo effect could be subtracted from the total effect in order to determine the true treatment value of the investigational drug. Similar experimental design logic is used in many laboratory procedures. Beecher regarded the placebo as a “blank” condition used to assess the “background noise” in drug studies. Changes in the symptom, disease, or disorder of interest not attributable to the investigational treatment were subsumed under the placebo effect category irrespective of the cause, because the “nonspecific causes” were, by definition, unknown.

Recently, critics have reviewed the reports that Beecher relied upon for his seminal paper and concluded that the placebo effect that Beecher saw did not, in fact, exist. They argue that Beecher’s placebo effect was the product of factors such as sloppy research, misinterpretation or misreporting of other’s data, natural history of the disease, or statistical regression to the mean (Kienle & Kiene, 1996; Kienle & Kiene, 1997). Others hold an opposite view. A Trans-National Institutes of Health/Department of Health and Human Services workshop entitled “The Science of the Placebo: Toward an Interdisciplinary Research Agenda” questioned the very concept of the placebo effect as a baseline condition, but for a very different reason (NIH, 2000). Among the attendees, the placebo effect was regarded more as Beecher saw it, as a very active and sometimes very powerful mind-body phenomenon. The NIH sponsors called for an interdisciplinary research agenda to help define the



mechanisms of the placebo effect and examine possible applications of what might be called “placebo therapy.” Once the mechanisms are understood, some attendees suggested, the very term “placebo” might cease to exist.

This type of analysis may open a scientific Pandora’s Box as far as traditional medical research methodology is concerned. It should be of great interest to clinical psychophysiology in general, and to those interested in clinical applications of EEG operant procedures (“neurotherapy”) in particular. The placebo effect has been used as a “nonspecific” baseline against which drug therapies (and other treatments) can be compared, much as Beecher recommended. In more common experimental design terminology, the placebo effect is neither a dependent nor independent variable. It is free to vary independently of the experimental variables as an uncontrolled variable in order to function as a baseline. It is assumed that the placebo effect is present at the same magnitude in the investigational arm as in the placebo arm. No one knows if that assumption is correct.

The placebo effect can also be seen as an experimental dependent variable. In fact, some studies have shown that the strength of the placebo effect (dependent variable) can be manipulated as a function of the route of administration of the placebo agent (e.g., injected vs. oral), color of the placebo agent, and so forth. Thus, aspects of the placebo condition can be manipulated experimentally (Ader, Grotta, & Cohen, 1987; Wickramasekera, 1998). A brochure recently sent out by a research institute announcing a workshop in psychopharmacology included a panel discussion entitled “Influencing the Placebo Response.” As the mechanisms underlying the placebo effect are more clearly understood it will no longer be possible to call it a “nonspecific” phenomenon.

One presenter at the NIH Placebo Conference questioned the assumption that the placebo effect is a feature upon which the “true” treatment effect is superimposed in an additive fashion. She suggested that another possibility is that the placebo effect is a process that dynamically interacts with and modifies the investigational treatment effect (Harrington, 2000). Remember, Beecher observed that there were times that a placebo effect could *reverse* pharmacological effects. If the placebo response is interactive with the investigational treatment, then the placebo effect cannot be used as a meaningful baseline comparator to determine the “true” effect of an investigational treatment. Further, once the mechanisms of the placebo effect are known, the placebo mechanism too will be subject to sophisticated manipulation, and the

placebo effect will simply become another dependent variable to be studied in systematic fashion.

The construct of the “placebo effect” may actually have limited scientific value as a baseline measure once the mediating factors are identified. Currently, the term refers to clinical outcomes resulting from uncontrolled variables that operate in an unknown manner. It is a label appended to a construct that gives an appearance of scientific rigor where none exists. In any particular placebo controlled study, the magnitude of the placebo effect itself is measured, and the magnitude of the placebo effect “plus” the investigational treatment effect is measured, but the magnitude of the “pure” investigational treatment effect can never be known, unless the placebo effect can be completely neutralized. Theoretically that might be accomplished using an unusual (and very unethical) procedure, such as secretly administering an investigational drug to patients without their knowledge or consent.

Such a study was actually carried out in 1988 in France before their regulations required “systematic” informed consent (Bergmann et al., 1994). Patients suffering from mild to moderate cancer pain (not requiring narcotic drugs) were randomized into one of two arms of a placebo controlled study of naproxen. Members of one group were informed that they would receive either placebo or naproxen in a randomized crossover study. Members of the second group were not informed that they were in such an experiment. They received either naproxen or placebo using the same dosage and crossover design, but were given information only about naproxen. They did not know they would also receive placebo. The outcome measure was the amount of change in pain reported before (i.e., “time zero”) and 30, 60, 120, and 180 minutes after drug or placebo administration. The measurement instrument was a 100mm Huskison’s visual analog scale (VAS) where a value of 0 = “no pain at all” and 100 = “pain as bad as it could be.” By the 180-minute assessment, the informed naproxen group reported a pain decrease ( $22.1 \pm 30.5$ ) much greater than the uninformed naproxen group ( $5.3 \pm 34.4$ ). The informed placebo group experienced pain relief almost as great as the informed naproxen patients ( $19.2 \pm 21.3$ ), while the uninformed placebo group experienced no analgesia ( $-8.5 \pm 35.5$ ). The negative value means an increase in pain scores compared to “time zero.” The authors used the study to express concern about the “less accurate” evaluation of the active drug’s analgesic efficacy compared to placebo (22.1 vs. 19.2) as a function of informed consent. In fact, it can be seen that information about participation in the study greatly en-

hanced the analgesic effect of both drug and placebo, such that it appears that most of the analgesic effect of the active drug can be attributed to the concurrent placebo effect! The authors suggested, “Without information about the study, analgesic effect might be ‘purer’ without interaction due to the design of the trial” (Bergmann et al., 1994, p. 46).

Results such as this suggest that Harrington’s hypothesis suggesting a dynamic interaction between investigational treatment and placebo (rather than the simple additive effect proposed by Beecher) has merit. Awareness of treatment appears to be a significant factor in the “efficacy” of both active treatment and placebo for certain disorders. Might we expect to encounter arguments about the ethics of not *maximizing* the therapeutic advantages of the “placebo response,” much as there have been debates about the ethics of withholding known treatments in current placebo controlled RCT’s (Glaros, 2001; La Vaque & Rossiter, 2001a; La Vaque & Rossiter, 2001b; Lurie, 1999; Rothman, 1987; Rothman, 2000; Striefel, 2001; WMA, 2000)? Basmajian, for instance, has already suggested that the terminology should be changed from “placebo” (“I will please”) to “debonafide” (“from good faith”) when the mind-body influences are manipulated purposely for therapeutic purposes (Basmajian, 1999). Identifying the mechanisms that mediate the placebo effect is one of several factors that will be particularly relevant to clinical psychophysiology, since by definition the discipline relies upon the study of mind-body interrelationships, and the relevant variables should be quantifiable (La Vaque, 1999).

If the placebo effect actually is mediated by a mind-body or mind-behavior process, it must be recognized that is exactly what psychophysiology studies, and there seems to be something logically inconsistent about using a placebo control to study a psychophysiological event, since they are just different labels for the same process. The logic of the designs must be carefully considered. The disciplines of experimental psychophysiology and clinical psychophysiology should be prepared to actively participate in the process, but the discipline of psychophysiology has yet to gain the attention of the financially and politically more powerful and reductionistic disciplines. As an example, despite the mind-body therapy emphasis of our discipline, the term “psychophysiology” was never used at the NIH Placebo Conference (NIH, 2000).

The discipline of psychophysiology is in a unique position, studying the very “stuff” of the mind-body dynamic, and so it does not fit precisely into the model of either somatic therapies or psychological therapies. We have to sail carefully between the Scylla of uncritical acceptance of scien-

tific orthodoxy and the Charybdis of ethical mandate. A study may, after all, be scientifically sound but ethically unacceptable. Professional organizations such as the Society for Neuronal Regulation (SNR), the Association of Applied Psychophysiology and Biofeedback (AAPB), and the American Psychological Association (APA) should, at a minimum, review the ethical and experimental design issues raised by the Declaration of Helsinki, and be prepared to offer guidance to their members.

### SUMMARY

The randomized placebo controlled double blind (RCT) design for the study of investigational treatments has been so accepted that it has become the “placebo orthodoxy.” There have been serious challenges to the placebo control design on both ethical and functional grounds, both of which have important implications for studies in applied psychophysiology. The Declaration of Helsinki prohibits the use of placebo controls for the study of disorders for which known treatments exist, yet standard medical treatments already exist for most, if not all, of the disorders of interest to applied psychophysiology. Placebo controls will continue to be acceptable when the *assay sensitivity* of the measure is poor (i.e., when the strength of the treatment effect is poor) or when no effective standard therapy is available for the disorder of interest. Alternative designs are available (such as the active control design), but each alternative carries with it a statistical analysis requirement that must be recognized.

The nature of the placebo response itself has come under scrutiny. The National Center for Complimentary and Alternative Medicine (NCCAM) and an NIH “Trans-National Institutes” workshop has issued a call for the study of the mind-body mechanisms underlying the placebo response. This paper suggests that the legitimacy of the placebo response as a baseline against which a “true” treatment effect can be measured has been brought into question. It is important for professional organizations interested in the psychophysiology of healing to examine the ethical and experimental design issues.

### REFERENCES

- Ader, R., Grota, L. J., & Cohen, N. (1987). Conditioning phenomena and immune function. *Annals of the New York Academy of Science*, 496, 532.
- Arnold, L. E. (November 16-18, 1998). *Treatment alternatives for attention deficit hyperactivity disorder*. Paper presented at the NIH Consensus Development Confer-

- ence on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder, Bethesda, MD.
- Barkley, R. A. (1992). Is EEG biofeedback treatment effective for ADHD children? *Ch.A.D.D.er Box*, 5-11.
- Basmajian, J. V. (1999). The third therapeutic revolution: Behavioral medicine. *Applied Psychophysiology and Biofeedback*, 24 (2), 107-116.
- Beecher, H. K. (1955). The powerful placebo. *Journal of the American Medical Association*, 159 (17), 1602-1606.
- Bergmann, J. F., Chassany, O., Gandiol, J., Deblois, P., Kanis, J. A., Segrestaa, J. M., Caulin, C., & Dahan, R. (1994). A randomised clinical trial of the effect of informed consent on the analgesic activity of placebo and naproxen in cancer pain. *Clinical Trials and Meta-Analysis*, 29 (1), 41-47.
- Blackwelder, W. C. (1982). "Proving the null hypothesis" in clinical trials. *Controlled Clinical Trials*, 3 (4), 345-353.
- Duffy, F. H. (2000). The state of EEG biofeedback therapy (EEG operant conditioning) in 2000: An editor's opinion. *Clinical Electroencephalography*, 31 (1), V-VIII.
- FDA. (1996a). ICH E3. Guidelines for industry: Content and structure of clinical study reports. [Online]. Available: <http://www.fda.gov/cder/guidance/index.htm>
- FDA. (1996b). ICH E6. Guidance for industry: Good clinical practice. [Online]. Available: <http://www.fda.gov/cder/guidance/index.htm>
- FDA. (1997). ICH E8. General considerations for clinical trials. [Online]. Available: <http://www.fda.gov/cder/guidance/index.htm>
- Fenger, T. N. (1998). Visual-motor integration and its relation to EEG neurofeedback brain wave patterns, reading, spelling, and arithmetic achievement in attention deficit disordered and learning disabled students. *Journal of Neurotherapy*, 3 (1), 11-20.
- Freedman, B., Glass, K. C., & Weijer, C. (1996). Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. *Journal of Law, Medicine & Ethics*, 24 (3), 252-259.
- Freedman, B., Weijer, C., & Glass, K. C. (1996). Placebo orthodoxy in clinical research. I: Empirical and methodological myths. *Journal of Law, Medicine & Ethics*, 24 (3), 243-251.
- Freeman, T., Vawter, D., Leaverton, P., Godbold, J., Hauser, R., & Goetz, C. (1999). Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. *New England Journal of Medicine*, 341, 988-992.
- Fu, W. K. (2000). Re: Randomized controlled trials in surgery: An essential component of scientific progress (*Spine* 1999; 24:2553-5) [letter; comment]. *Spine*, 25 (15), 2002-2004.
- Fuchs, T. (1999). *Aufmerksamkeit und neurofeedback: Evaluation eines psychophysiologischen eeg-biofeedback-behandlungs programms bei aufmerksamkeits und hyperaktivitätsstörungen in kinsalter (Attention and neurofeedback: An evaluation of a psychophysiological EEG biofeedback treatment program for childhood attention-deficit/hyperactivity disorders)*. Regensburg: Roderer.
- Glaros, A. G. (2001). A comment on La Vaque and Rossiter. *Applied Psychophysiology and Biofeedback* 26(1), 61-65.

- Hammerschlag, R. (1998). Methodological and ethical issues in clinical trials of acupuncture. *Journal of Alternative and Complementary Medicine*, 4 (2), 159-171.
- Harrington, A. (2000, November 19-21). "Seeing" the placebo effect: Historical legacies and present opportunities. Paper presented at The Science of the Placebo: Toward an Interdisciplinary Research Agenda, National Institutes of Health, Bethesda, MD.
- Jarrett, R. B., Schaffer, M., McIntire, D., Witt-Browder, A., Kraft, D., & Risser, R. C. (1999). Treatment of atypical depression with cognitive therapy or phenelzine: A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, 56 (5), 431-437.
- Kienle, G. S., & Kiene, H. (1996). Placebo effect and placebo concept: A critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Alternative Therapies in Health and Medicine*, 2 (6), 39-54.
- Kienle, G. S., & Kiene, H. (1997). The powerful placebo effect: Fact or fiction? *Journal of Clinical Epidemiology*, 50 (12), 1311-1318.
- La Vaque, T. J. (1999). Neurotherapy and clinical science. *Journal of Neurotherapy*, 3 (3 & 4), 29-31.
- La Vaque, T. J., & Rossiter, T. R. (2001a). The ethical use of placebo controls in clinical research: The Declaration of Helsinki. *Applied Psychophysiology and Biofeedback*, 26(1), 23-37.
- La Vaque, T. J., & Rossiter, T. R. (2001b). Response to Striefel and Glaros. *Applied Psychophysiology and Biofeedback*, 26(1), 67-71.
- Levin, J. S., Glass, T. A., Kushi, L. H., Schuck, J. R., Steele, L., & Jonas, W. B. (1997). Quantitative methods in research on complementary and alternative medicine. A methodological manifesto. NIH Office of Alternative Medicine. *Medical Care*, 35 (11), 1079-1094.
- Lurie, P. (April 21, 1999). *The use of placebos in clinical trials and the ethics of the use of placebos*. Paper presented at the Committee for Advanced Scientific Education Seminar Series, Rockville, MD.
- Lurie, P., & Wolfe, S. (1997). Unethical trials of interventions to reduce perinatal transmission of the Human Immunodeficiency Virus in developing countries. *New England Journal of Medicine*, 337 (12), 853-856.
- Macklin, R. (1999). The ethical problems with sham surgery in clinical research. *New England Journal of Medicine*, 341 (13), 992-996.
- McNeill, P. M. (1998). Should research ethics change at the border? (editorial). *The Medical Journal of Australia*, 169, 509-510.
- NCCAM. (Winter, 2000). NCCAM Advisory Council reviews first year: Striving for excellence in CAM research. *Complimentary and Alternative Medicine at the NIH*, 7, 1-8.
- NIH. (November 19-21,2000). *The science of the placebo: Toward an interdisciplinary research agenda*, Natcher Conference Center, Bethesda, MD.
- Norris, S. L., Lee, C., Cea, J., & Burshteyn, D. (1998). Performance enhancement training effects on attention: A case study. *Journal of Neurotherapy*, 3 (1), 21-27.
- Quitkin, F. M. (1999). Placebos, drug effects, and study design: A clinician's guide. *American Journal of Psychiatry*, 156 (6), 829-836.

- Ramos, F. (1998). Frequency band interaction in ADD/ADHD neurotherapy. *Journal of Neurotherapy*, 3 (1), 28-46.
- Ramsay, S. (1999). More developments in developing-world research ethics (news). *Lancet*, 354 (9188), 1405-1406.
- Rossiter, T. R., & La Vaque, T. J. (1995). A comparison of EEG biofeedback and psychostimulants in treating attention deficit hyperactivity disorders. *Journal of Neurotherapy*, 1 (1), 48-59.
- Rothman, D. J. (1987). Ethical and social issues in the development of new drugs and vaccines. *Bulletin of the New York Academy of Medicine*, 63 (6), 557-568.
- Rothman, K. J. (2000). Declaration of Helsinki should be strengthened. *British Medical Journal*, 321 (7258), 442-445.
- Rothman, K. J., & Michels, K. B. (1994). The continuing unethical use of placebo controls. *New England Journal of Medicine*, 331 (6), 394-397.
- Striefel, S. (2001). Ethical research issues: Going beyond the Declaration of Helsinki. *Applied Psychophysiology and Biofeedback*, 26(1), 39-59.
- Temple, R. (April 21, 1999). *The use of placebos in clinical trials and the ethics of the use of placebos*. Paper presented at the Committee for Advanced Scientific Education Seminar Series, Rockville, MD.
- Temple, R., & Ellenberg, S. S. (2000). Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Annals of Internal Medicine*, 133 (6), 455-463.
- Wadhvani, S., Radvanski, D. C., & Carmody, D. (1998). Neurofeedback training in a case of attention deficit hyperactivity disorder. *Journal of Neurotherapy*, 3 (1), 42-49.
- Wickramasekera, I. (1998). Secrets kept from the mind but not the body or behavior: The unsolved problems of identifying and treating somatization and psychophysiological disease. *Advances in Mind-Body Medicine*, 14, 52.
- WMA. (2000). *The Declaration of Helsinki*. Paper presented at the 52nd WMA General Assembly, Edinburgh, Scotland.
- Woodman, R. (1999). Storm rages over revisions to Helsinki Declaration [news]. *British Medical Journal*, 319 (7211), 660.