Placebo-Controlled Procedural Trials for Neurological Conditions

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Summary: Neurological disease has been a central focus in the ongoing ethical debate over the use of invasive placebo controls, especially sham surgery. The risk to research subjects and necessary use of deception involved in these procedures must be balanced against the methodological need to control for bias and the placebo effect. We review a framework formulated for the ethical assessment of sham surgery in the context of research evaluating novel procedures for neurological conditions. Special issues raised include the growing evidence of expectation and conditioning effects in a number of neurological diseases, the escalating scale of risk from different types of invasive placebo interventions, and the increasing use of cross-over designs, which allow a switch from placebo to active intervention without additional procedures. **Key Words:** Placebo-controlled trials, sham surgery, cross-over, ethics, neurological procedures, deception.

INTRODUCTION

The ethical debate on sham surgery has intensified in the past decade, particularly in response to placebo-controlled trials of dopaminergic cell transplantation for Parkinson's disease (PD).[1–4] Ethical discourse on placebo or sham surgery was initiated in a 1961 commentary by Henry Beecher, who argued for its utility in randomized trials to control for evaluator bias and the placebo effect.[5] Sham surgery under double-blind conditions exposed mammary artery ligation as no more effective than a placebo intervention in treating angina.[6,7] In 2002, a sham-controlled trial of arthroscopic lavage and debridement for osteoarthritis of the knee similarly discredited an invasive and costly procedure.[8] Using these trials as examples, we formulated a framework for the ethical assessment of placebo surgery.[9–11] Despite an increase in the acceptance and design of sham-controlled surgical trials among physician-scientists,[12,13] ethical opposition has mounted on issues of scientific necessity and the level of risk posed to patient-subjects.[14,15]

Neurological procedure trials have been at the forefront of this discussion primarily for two reasons. First, neurological procedures range from minimally to critically invasive and may involve conditions of a highly emergent nature. Sham controls at the extreme end of this spectrum may pose a risk of death and irreversible sensory, cognitive, or motor dysfunction. Second, evidence for the placebo effect and an understanding of its mechanisms are emerging for various neurological conditions including pain, depression, and motor disorders such as PD.[16] In these conditions, the parts of the nervous system subject to disease may be modulated directly by expectation and/or conditioning. These placebo effects must be controlled for in order to dissociate these processes from those reflecting the efficacy of a given procedure. In addition, blinding patient-subjects to the treatment they receive is necessary to avoid bias in trials evaluating subjective outcomes (which are common in neurological research).

The goal of this article is to elaborate on our ethical framework for sham invasive procedures, with a special emphasis placed on highly invasive procedures for neurological conditions. We will review six benchmarks for the justification of sham surgery, with examples from the literature that represent critical points along a spectrum of risk.

METHODOLOGICAL JUSTIFICATION

Commentators opposing the use of sham surgery argue that it violates the principle of nonmaleficence in posing risk to research participants without the prospect of direct benefit.[2,3,24,17] Unlike inert pharmaceutical pla-

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cebos, invasive sham surgery may involve risks associated with surgical incision, general anesthesia, and immunosuppression. This objection is not valid, however, because it conflates the ethics of clinical care with the ethics of clinical research.[9,18] Whereas the aim of clinical care is to maximize the health and well-being of particular patients, the goal of research is to acquire clinically relevant knowledge that will benefit future patients.[9] In clinical research, there is no requirement to offer participants the prospect of direct benefit or to ensure the absence of risk. Indeed, critical areas of biomedical research, including Phase I toxicity testing and studies of pathophysiology, expose participants to risk without the prospect of direct benefit. This research is necessary in order to translate medical innovation into safe and effective treatments.

Reliable data on the efficacy of novel interventions, whether pharmaceutical or procedural, enables physicians to choose the most effective among treatment options and avoid the risks and unnecessary cost of inferior or ineffective treatments. In clinical trials, the control arm to which a novel intervention is compared is critical to the evaluation of its efficacy. Sham surgery controls for four factors that can lead to false positives: 1) investigator bias during unblinded evaluation, especially when outcomes involve subjective rating scales, 2) patient-subject bias in unblinded reporting, 3) the placebo effects of expectation or conditioning, and 4) any additional therapeutic effects due to processes unrelated to the hypothesized mechanism of the active intervention. In many cases, sham surgery is the only way to ensure rigorous control for these confounding factors.

Double-blinding is especially important in neurological trials, because outcome measures often involve ratings with a degree of subjectivity, as with pain, depression, motor function, and quality of life.[19] Controlling for the placebo effect associated with invasive neurological procedures is also critical, because expectation may alter neurological outcomes in significant ways. Expectation of treatment alone has been shown to modulate a diversity of physiological processes, including a decrease in blood flow to pain-processing brain areas in healthy subjects subjected to painful stimuli, a decrease in activity in neurons of the subthalamic nucleus correlated with increased motor performance in PD patients, and an increase in striatal dopamine release in PD patients.[20–22]

Conditioning may contribute an additional therapeutic effect. It has been shown, for example, that associating a flavored drink with cyclosporin A leads to conditioned immunosuppression in human subjects.[23] Patient-subjects in neurosurgical trials, such as those for PD, have potentially experienced repeated clinical treatments or research trial interventions.[24] These individuals may be conditioned to respond therapeutically to procedures included in a clinical trial, or conversely, they may harbor lowered expectations for any future interventions, however novel.

Finally, nonspecific effects of a procedure, such as lesioning due to electrode placement for deep brain stimulation in epilepsy, have been shown to have therapeutic effects in themselves.[25] Thus, there is often no effective alternative to sham surgery that will effectively blind the evaluation and reporting of neurological symptoms from bias and also control for the nonspecific effects of the procedure and the neuromodulatory effects of expectation and conditioning.

These methodological considerations are ethically relevant. The risks to which research subjects are exposed cannot be justified unless the research design is scientifically valid and thus has the potential to produce clinically valuable knowledge.[26]

ETHICAL EVALUATION OF RISKS AND BENEFITS

Despite sound scientific reasons for sham-controlled trials of neurological procedures, patient-subjects must be protected from excessive risk. In the context of clinical research, risk must be minimized and balanced by the prospect of direct benefit and/or the knowledge to be gained from the study.[26] As mentioned above, sham surgery typically exposes subjects to the risk of an invasive procedure without the potential of direct benefit from the active intervention. However, patient-subjects in the sham arm also forgo the potential risks of the active intervention, which may include hemorrhage and/or infection from dural penetration during implantation or lesion operations, dyskinesia from deep pallidal stimulation for PD, or nausea and/or anorexia from pallidal infusion of glial cell line-derived neurotrophic factor (GDNF) in PD patients.[27–29] Thus, sham surgery should not be assumed a priori to present a less favorable risk–benefit ratio than the active arm.

Patient-subjects in the sham and active arms encounter different risk–benefit ratios, and these should be assessed and justified independently. The former are exposed to risks of the sham surgery that are balanced not by personal benefit but by the importance of clinically useful data, the interpretation of which necessitates a placebo control. The latter are exposed to risks of surgery and active treatment that are balanced by the prospect of direct benefit, as well as the clinical value of the data.

Given the absence of direct benefit other than the potential therapeutic benefit of the placebo effect and other nonspecific aspects of the procedure, what level of risk in sham surgery is ethically acceptable? A reasoned principle specifying the upper limit on acceptable risk in clinical research has yet to be effectively formulated, if one exists at all, and we recommend a case-by-case process of deliberation and judgment. As a first step,

TABLE 1. *Escalating Risk in Placebo-Controlled Trials for Neurological Procedures*

Trial or Procedure (Reference)	Placebo Control	Risk–Benefit	Ethically Acceptable?
Transcranial magnetic stimulation for epilepsy (Fregni et al.[31,32,34]; Solo-Padulles et al.[33])	Placement of coils over skull without stimulation	No risk, no prospect of benefit from active intervention	Yes
Acupuncture for migraine (Linde et al.[35])	Fine-needle stimulation, no manual stimulation	Very low risk, no prospect of benefit from active intervention	Yes
Deep brain stimulation for primary dystonia (Kupsch et al.[28])	Implantation of device, no stimulation, possibility of cross-over after trial	Penetration of dura, device implantation, prospect of direct benefit in cross-over to active intervention	Yes
Cell transplantation for Parkinson's disease (Freed et al.[1]; Olanow et al.[37])	Bilateral full burr holes into skull	No penetration of dura, local anesthesia, no prospect of benefit from active intervention	Yes
Intracranial drug infusion for Parkinson's disease (Nutt et al.[29]; Lang et al.[38])	Catheter implantation, infusion of saline	Penetration of dura, device implantation, continual risk of infection, hemorrhage, and dislodgment during placebo infusion, prospect of direct benefit in cross-over to active intervention	?
Bypass surgery and laser perforation for aneurysm in arteriovenous malformation (Grady[39])	Not designed	Emergent condition, withholding intervention is life threatening	No

risks of the sham procedure should be compared to the threshold of acceptable risks posed in other areas of research that offer little or no prospect of direct benefit, such as Phase I toxicity testing, or natural history studies involving diagnostic procedures, such as biopsies, lumbar puncture, or bronchoscopy.[10] Next, a careful assessment of whether known and unknown risks from the novel procedure are acceptable should be performed by the investigators and institutional review board, possibly with consultations from patient advocates and members of the public.

A useful operational approach to risk assessment proposed by London[30] recommends that equal consideration be given to the interests of subjects bearing the burden of research risks and to the interests of the individuals who will eventually receive the benefits of the knowledge to be gained. Here we will review six recent examples that illustrate the spectrum of risk–benefit considerations in sham controls of neurological trials (Table 1). Critical factors in the ethical assessment of risk are highlighted.

EXAMPLES OF ESCALATING RISK

Transcranial magnetic stimulation

A number of studies have tested the efficacy of transcranial magnetic stimulation in treating epileptic seizures, motor function after stroke, and memory after cognitive decline.[31–33] A noninvasive procedure delivering magnetic pulses to the cortex, transcranial magnetic stimulation decreases cortical excitability using high-frequency stimulation and increases cortical inhibition using low-frequency stimulation. A related technique, transcranial direct stimulation, applies weak DC electrical current to the cortex; it has been tested in sham-controlled trials for traumatic spinal cord injury.[34] Sham application of both techniques involves placement of coils or electrodes over the skull, with either a diversion of magnetic pulses or current away from the skull or a complete absence of stimulation. These procedures are noninvasive and pose very little risk.

Acupuncture

In 2006, Linde et al.[35] conducted a randomized, sham-controlled trial of acupuncture to prevent migraine headaches in patients suffering from two to eight attacks per month. In the sham arm, patient-subjects received fine-needle insertion, but no manual stimulation, at non–acupuncture points. This sham procedure involved minimal invasiveness and the level of risk was minimized. Ethical issues of deception are raised, in that subjects were not informed that they had a chance to receive a placebo intervention[36] and administration of the sham required extensive deception as the acupuncturist pretended to perform valid procedures. These issues will be discussed later.

Deep brain stimulation

Implantation of devices producing high-frequency neurostimulation allows for a cross-over design in which all patient-subjects receive the activated device. Those randomized to placebo (no stimulation) may be switched to active treatment after the end of a blinded evaluation

period. A 2006 sham-controlled cross-over trial tested the therapeutic efficacy of pallidal deep brain stimulation in patient-subjects with primary dystonia.[28] All participants received bilateral surgical implantations of a quadripolar electrode device under general anesthesia. Surgery penetrated the dura, but the ability to control device settings offered both the active and placebo group a prospect of direct benefit. Patient-subjects in the placebo arm were exposed to the full risks of a complete implantation surgery, which included infection and seroma, but also received the prospect of direct benefit after a 3-month blinded evaluation period.

Trials with this design pose a reasonable level of risk to subjects in the sham arm: invasiveness of device implantation is balanced by prospect of direct benefit. The placebo group experiences a delay in receiving a potentially useful treatment, but also avoids any unknown risks of the active treatment, which in the cited case included dysarthria and dysesthesias, until data on efficacy has been collected. An on–off cross-over design that allows for a switch from the sham to active intervention without additional procedures permits greater risk than designs that lack this feature, given the prospect of benefit from the active intervention.

Cell transplantation

There have been two published sham-controlled trials of human fetal dopaminergic cell transplantation into the putamen of PD patients.[1,37] Placebo surgery involved burr holes into the skull, with no penetration of dura. One trial administered local anesthesia alone, with no immunosuppression; the other used general anesthesia and immunosuppressive treatment. In both trials, risk of the sham surgery was minimized by limiting the invasiveness of the procedure to burr holes sufficient to maintain the double-blind and control for the placebo effect of expectation, which has been characterized in biochemical, neurophysiological, and behavioral assays in patients with PD. Nonspecific effects of the more invasive injection procedure were not controlled for, but were appropriately judged in this case as unlikely to contribute any therapeutic mechanism alone.

This type of trial design, involving a moderately invasive sham surgery without penetration of the dura, was judged to pose an acceptable level of risk in nonbeneficial research by 90.2% of investigator members of the Parkinson's Study Group.[12] Moreover, the clinical importance of using a randomized, sham-controlled trial to test fetal dopaminergic grafting is underscored by the negative results obtained, which counter earlier positive results from open-label trials.[27] The demonstrated lack of efficacy in the tested protocols has driven the field forward to make changes to improve the technique.

Intracranial drug infusion

Catheter implantation is a general technique for allowing targeted drug delivery to dysfunctional regions of the brain. Two sham-controlled trials have been conducted to test the efficacy of glial-cell-derived neurotrophic factor (GDNF) infusion into the cerebral ventricles or putamen of PD patients. In these trials, the sham arm involves saline infusions through a surgically implanted catheter to control for bias and the placebo effects of expectation.[29,38] Surgical implantation also controlled for nonspecific effects of catheter placement into the putamen or cerebral ventricles.

Patient-subjects in the placebo group were allowed to cross over to active GDNF infusion at the end of the trial if indicated. As with device implantation for deep brain stimulation, catheter placement is invasive past the dura; however, maintenance and continual use of the catheter poses additional risks of infection, hemorrhage, and dislodgment. Although all patient-subjects received eventual prospect of direct benefit, the time before cross-over in which the sham group was exposed to these substantial risks without the prospect of direct benefit carries a heavy burden of proof and may exceed a threshold of acceptable risk.

Bypass surgery

Invasive surgeries with critically emergent outcomes are not appropriate for sham-controlled trials. An example is a novel artery ligation and laser perforation procedure to prevent the pending rupture of an aneurysm in patients with arteriovenous malformation.[39] This surgery allows for a bypass graft to be ligated without clamping the artery, which imposes the risk of ischemia and subsequent brain damage during ligation. The risks of this invasive and life-threatening surgery are justified by the prospect of direct benefit during an emergent state of a potential aneurysm rupture. The decision to operate is made when the risks of withholding active intervention are judged greater than those of the operation. Because the active intervention would never be tested in a nonemergent context, a sham control, however minimally invasive, would exceed an acceptable level of risk by withholding treatment.

INFORMED CONSENT AND THE USE OF DECEPTION

In addition to risk, ethical concern over the use of deception in administering sham procedures has been raised.[2] Unlike pharmacologic placebos, sham procedures and surgery sometimes require that an investigator actively mislead participants into believing that the active intervention is being performed, in order to maintain the blind and control for the placebo effect. In the sham acupuncture trial published by Linde et al.,[35] acupunc-

turists were trained to perform the sham procedure with oral instructions, a videotape, and a brochure. In the Freed et al.[1] study of fetal cell transplantation in PD patients, subjects receiving sham surgery were awake under local anesthesia and were asked if they were "ready for the implant."

Active deception on the part of investigators appears to violate clinical research requirements of informed consent and respect for subjects, including the autonomous decision to participate in research.[27] Authorized deception, a process by which patient-subjects are informed of the possibility of deception in trial participation and of the risks involved with this deception, is an effective way to maintain informed consent and respect for autonomous decision making while effectively controlling for expectation effects.[40] Indeed, previously published guidelines for the use of deception include an authorization process in which the use of misleading tactics is disclosed during informed consent.[41]

To promote informed consent in sham-controlled trials, we recommend that subjects be clearly informed about the placebo arm and that they will have a 50% or less chance of receiving a fake procedure for the purpose of a scientifically valid evaluation of the effectiveness of the real procedure. The arthroscopic knee surgery trial conducted by Moseley et al.[8] used a similar consent process, in which subjects were required to write out a statement referring to the possibility that they might receive a placebo procedure. As an additional safeguard to ensure full understanding of both randomization to placebo and the use of active deception to mask the placebo (or treatment), it may be desirable for a clinician independent of the research team to obtain informed consent. Existing studies have shown no difference in expectation effects between subjects consenting under authorized deception and unauthorized deception, although effects may exist and vary by trial type and could be addressed with further study.[42] Further guidelines require that the misleading is necessary for the scientific aims of the study, that risks and the use of sham controls are specified, and that debriefing is made at the end of the trials.[43]

In cases in which potential patient-subjects may lose decision-making capacity, we recommend that participation in sham-controlled trials be limited to those who are capable of giving consent.

ETHICAL FRAMEWORK FOR JUSTIFYING THE USE OF PLACEBO PROCEDURES AND SURGERY

Placebo-controlled trials for neurological procedures should be justified using the following benchmarks formulated for sham surgery: 1) the research design addresses a valuable, clinically relevant question, 2) the placebo control is methodologically necessary and no sufficiently rigorous alternative design exists to address the study hypothesis, 3) the risk of the placebo is minimized, 4) the risk of the placebo arm does not exceed a threshold of acceptable research risk, 5) the risk of the placebo in the absence of prospect of direct benefit is justified by the clinical knowledge to be gained, and 6) the deception used to blind the placebo arm is disclosed to and authorized by participants.[10] Differences in ethical considerations of trial design for varying neurological conditions may stem from variations in 1) evidence for a placebo effect and necessity of a sham control if blinding may be maintained without sham surgery, 2) ability to create expectation while minimizing invasiveness of the placebo, 3) level of risk in the sham surgery, 4) ability to cross over to the active intervention without additional procedures, and 5) level of active deception involved in the sham administration.

CONCLUSION

Placebo-controlled trials are regarded as the gold standard in testing the efficacy of novel medical interventions, including drugs, devices, procedures, and surgery. In neurological procedures, subjective outcome measures and evidence for the neuromodulatory effects of expectation and conditioning necessitate a control arm that both protects an interpretation of results from evaluator and reporter bias and accounts for improvements due to the placebo effect. For these reasons, many researchers find sham surgical controls an ethically acceptable design when minimally or moderately invasive, such as in the use of burr holes to the skull with no pial penetration in trials of cell transplantation for PD.[12,13] Invasive interventions that penetrate the dura pose a risk of infection and hemorrhage and are not acceptable when there is no prospect of direct benefit.

Cross-over designs (in which surgical implantations of a device may be tested using an on-or-off state) increase the threshold of acceptable risk, because all patient-subjects receive the prospect of direct benefit. A cross-over design may exceed the threshold of acceptable risk if the participants in the placebo arm are exposed to significant and continual risk before cross-over to the active intervention. Critically emergent conditions should not be subject to a sham control.

In many cases, the level of risk in sham surgery must be balanced against the value of subjecting invasive procedures to rigorous, blinded evaluation. Risky procedures introduced into clinical practice despite being ineffective or costly may cause a comparable or greater harm to patients. We recommend the framework and special considerations described above in the ethical justification of sham surgery in trials for neurological procedures.

REFERENCES

1. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344:710–719.
2. Macklin R. The ethical problems with sham surgery in clinical research. N Engl J Med 1999;341:992–996.
3. Gillett GR. Unnecessary holes in the head. IRB Ethics Hum Rev 2001;23(6):1–6.
4. Albin RL. Sham surgery controls: intracerebral grafting of fetal tissue for Parkinson's disease and proposed criteria for use of sham surgery controls. J Med Ethics 2002;28:322–325.
5. Beecher HK. Surgery as placebo: a qualitative study of bias. JAMA 1961;176:1102–1107.
6. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med 1959;260:1115–1118.
7. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary artery ligation and sham operation for angina pectoris. Am J Cardiol 1960;5:483–486.
8. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81–88.
9. Horng S, Miller FG. Is placebo surgery unethical? N Engl J Med 2002;347:137–139.
10. Horng S, Miller FG. Ethical framework for the use of sham procedures in clinical trials. Crit Care Med 2003;31(3 Suppl): S126–30.
11. Miller FG. Sham surgery: an ethical analysis. Am J Bioeth 2003; 3:41–48.
12. Kim SY, Frank S, Holloway R, Zimmerman C, Wilson R, Kieburtz K. Science and ethics of sham surgery: a survey of Parkinson disease clinical researchers. Arch Neurol 2005;62:1357–1360.
13. Prehn AW, Vawter DE, Gervais KG, et al. Studying neurosurgical implants for Parkinson disease: a question of design. Neurology 2006;67:1503–1505.
14. Boer GJ, Widner H. Clinical neurotransplantation: core assessment protocol rather than sham surgery as control. Brain Res Bull 2002; 58:547–553.
15. Polgar S, Ng J. Ethics, methodology and the use of placebo controls in surgical trials. Brain Res Bull 2005;67:290–297.
16. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390–10402.
17. Weijer C. Comment: I need a placebo like I need a hole in the head. J Law Med Ethics 2002;30:69–72.
18. Litton P, Miller FG. A normative justification for distinguishing the ethics of clinical research from the ethics of medical care. J Law Med Ethics 2005;33:566–574.
19. Flum DR. Interpreting surgical trials with subjective outcomes: avoiding un SPORTsmanlike conduct. JAMA 2006;296:2483–2485.
20. Wager TD, Rilling JK, Smith EE, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 2004; 303:1162–1167.
21. Benedetti F, Colloca L, Torre E, et al. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. Nat Neurosci 2004;7:587–588.
22. De la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 2001;293: 1164–1166.
23. Goebel MU, Trebst AE, Steiner J, et al. Behavioral conditioning of immunosuppression is possible in humans. FASEB J 2002;16: 1869–1873.
24. De la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002;1:85–91.
25. Andrade DM, Zumsteg D, Hamani C, et al. Long-term follow-up of patients with thalamic deep brain stimulation for epilepsy. Neurology 2006;66:1571–1573.
26. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000;283:2701–2711.
27. Bjorklund A, Dunnett SB, Brundin P, et al. Neural transplantation for the treatment of Parkinson's disease. Lancet Neurol 2003;2: 437–445.
28. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355:1978–1990.
29. Nutt JG, Burchiel KJ, Comella CL, et al.; ICV GDNF Study Group. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 2003;60:69–73.
30. London AJ. Reasonable risks in clinical research: a critique and a proposal for the integrative approach. Stat Med 2006;25: 2869–2885.
31. Fregni F, Boggio PS, Valle AC, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke 2006;37: 2115–2122.
32. Fregni F, Otachi PT, Do Valle A, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. Ann Neurol 2006;60:447–455.
33. Sole-Padulles C, Bartres-Faz D, Junque C, et al. Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction: a randomized sham-controlled study. Cereb Cortex 2006;16:1487–1493.
34. Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 2006;122: 197–209.
35. Linde K, Streng A, Jurgens S, et al. Acupuncture for patients with migraine: a randomized controlled trial. JAMA 2005;293: 2118–2125.
36. Miller FG, Kaptchuk TJ. Acupuncture trials and informed consent. J Med Ethics 2007;33:43–44.
37. Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003;54:403–414.
38. Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann Neurol 2006;59:459–466 [Erratum in: Ann Neurol 2006;60:747].
39. Grady D. With lasers and daring, doctors race to save a young man's brain. The New York Times (Final ed.). Dec 19, 2006. Sect. F:1 (col. 1).
40. Miller FG, Wendler D, Swartzman LC. Deception in research on the placebo effect. PLoS Med 2005;2:e262.
41. Wendler D. Deception in medical and behavioral research: is it ever acceptable? Milbank Q 1996;74:87–114.
42. Weiner RL, Erker PV. The effects of prebriefing misinformed research participants on their attributions of responsibility. J Psychol 1986;120:397–410.
43. Miller FG, Kaptchuk TJ. Sham procedures and the ethics of clinical trials. J R Soc Med 2004;97:576–578.