Ethical Issues on the Frontiers Parkinson's Disease Research

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The big picture

What are the goals?

Research	Clinical Care
To advance scientific knowledge	First do no harm To provide the best standard of patient care

Research Ethics: an unsavory history

- Current regulation arose out of shameful examples of unethical research
  - Nazi human experiments
  - Henry K. Beecher article: 1966
  - Tuskegee syphilis study: 1932 – 1972
  - Willowbrook hepatitis experiment: 1963-66

Codes of research ethics

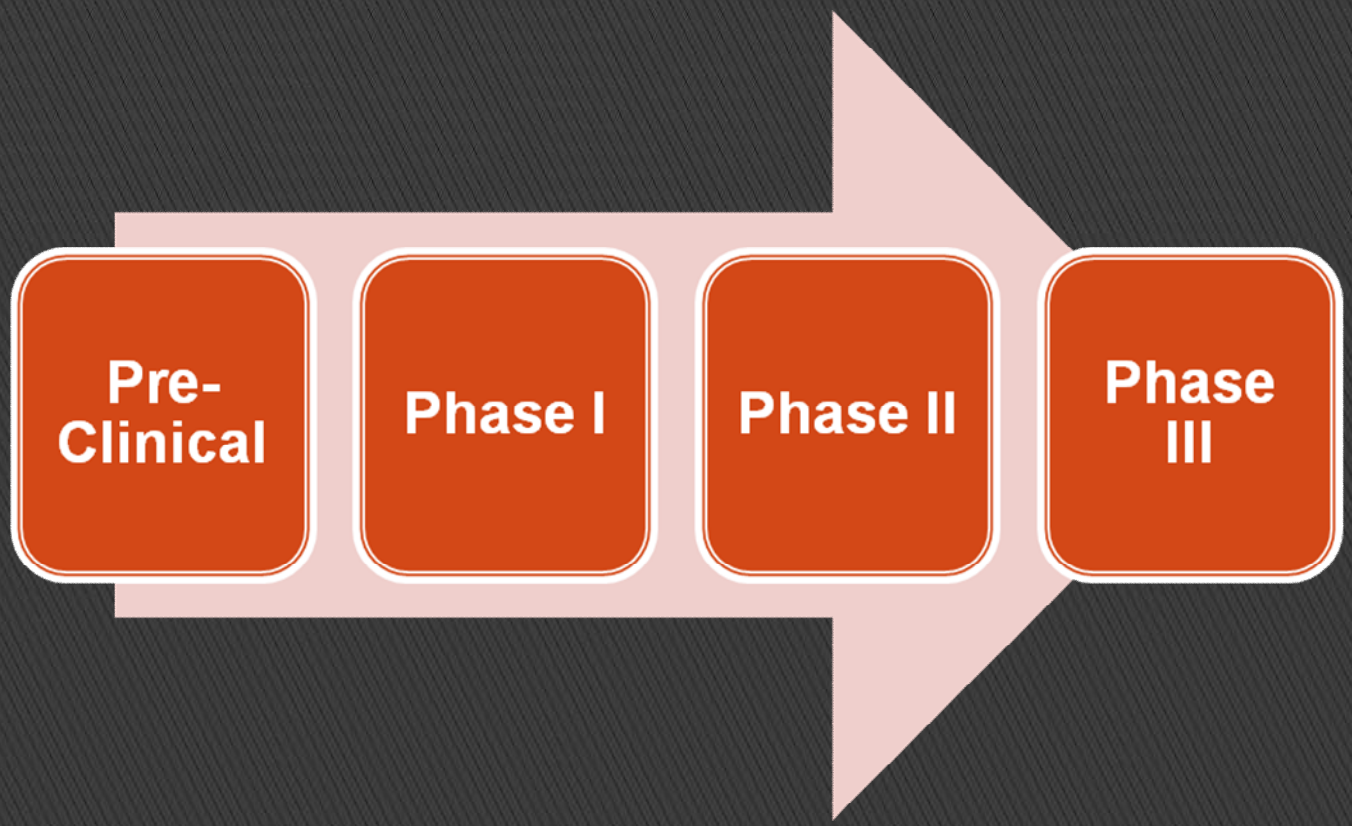
- International
  - Nuremberg Code of 1947
  - World Medical Association: Declaration of Helsinki – 1975, 1983, 1989, 2000
- United States
  - Belmont Report, 1978
  - Protecting Human Subjects, 1981

Understanding research design: *You* be the scientist

- How do you determine if transplantation of fetal nigral dopaminergic neurons into the brain is an effective treatment for Parkinson's disease?

Clinical Trials 101

What it takes to get a new medical or surgical treatment “to the market”:



Pre-Clinical studies

- Is this worth investigating in humans?
  - Test tube and animal studies –Preclinical studies demonstrate that implanted fetal nigral dopaminergic neurons can survive, manufacture dopamine, exhibit normal electrical firing patterns, reinnervate the striatum, form normal-appearing connections with host neurons, and improve motor function in parkinsonian rodents and primates

Phase I

- Is this safe in humans?
  - Uncontrolled open-label trials of fetal nigral transplantation in advanced PD patients are reported to provide clinically meaningful improvement in most, but not all, studies.

Phase II

- What dose is needed?
- How effective is the treatment?

WHY WASN’T THIS ANSWERED BY THE PHASE I STUDIES?

Placebo effect

- The beneficial effect in a patient following a particular treatment that arises from the patient's expectations concerning the treatment rather than from the treatment itself
- Placebos are used in clinical trials as a control to test the efficacy of new therapies
- Placebo effect is particularly strong in studies of pain interventions and in studies where the primary variable is a subjective and continuously varying measure

Placebo response in Parkinson's disease clinical trials is STRONG

- Placebo = >50% improvement in UPDRSm score or >2 pt increase on >2 UPDRSm items
- Medical trials: 14% of pts had + placebo response
- Surgical Trials: 42%

Placebo effect: the *special* case of Parkinson's disease

- Unlike most placebo effects, there may be an unique physiologic explanation for placebo effects in PD
  - Dela Fuente-Fernandez et al. studied the effect of placebo administration on dopamine release in PD subjects, and remarkably, placebo administration evoked substantial dopamine release
  - The effect on dopamine receptor occupancy was similar to parenteral administration of the DA apomorphine or oral levodopa

Trial Design

- How do you determine that the positive effect of surgical transplantation is not due to a placebo effect?

<u>Answer:</u>

A RANDOMIZED, PLACEBO-CONTROLLED, SURGICAL TRIAL

Randomized controlled trials: the special case of surgery

- Surgical procedures are often introduced into general practice on the basis of uncontrolled studies than for the approval of medical interventions → investigator bias, placebo effects
- Not surprising, and for good reason: how do you create a surgical placebo? (higher risk, ethically complex)

The Pertinent Questions:

- Under what circumstances are the risks to subjects assigned to the placebo group in a medical or surgical trials justified, and what risks are reasonable in order to determine the benefits and adverse effects of a given intervention?

The Danger of False Positive Results

- False positive trial results may admit into routine clinical practice procedures with little or no benefit and significant risks to patients
- Failure to control for placebo effect or investigator bias increases the risk of obtaining false positive results
- This point is *critical:*
  - False positive results represent an EXISTING HARM and by their continued acceptance, a FUTURE HARM to individual patients and to society at large

Surgery's Tainted History of False Positives

- Inadequately studied invasive or surgical procedures that became part of standard medical practice only to be abandoned after closer scrutiny:

Bloodletting
Lobotomy
Repeated cesarean delivery
Prophylactic portocaval shunting
Jejunoilial bypass for morbid obesity
Laparotomy for tuberculous peritonitis or PID
Adrenalectomy for essential hypertension
Internal-mammary-artery-ligation for angina
Extracranial-intracranial bypass for carotid artery occlusion
Gastric freezing
Routine circumcision
Glomectomy for asthma
Routine tonsillectomy

Estimating Effects: the case of the runaway Carotid Endarterectomy

- Used for decades as 1° and 2° stroke prophylaxis before rigorous scientific evaluation resulted in a decreased assessment of benefit and dramatically reduced the scope of pts in whom the benefits outweighed the risks of the procedure
- Hundreds of thousands of pts were exposed to unnecessary risks and substantial societal resources were wasted

Sham Surgery – the History

Even small trials incorporating sham surgery controls can have a major impact.

1959 - IMA Ligation for Angina

- The pioneering sham surgery studies were a pair of small randomized trials of internal mammary artery ligation for angina. These studies showed no specific benefit of IMA ligation at the time when the procedure was used regularly in clinical practice.
- In comments about the IMA ligation studies HK Beecher noted that two small, but well-constructed studies involving 35 pts probably spared thousands the risks of this unnecessary surgery.

2001: Knee Arthroscopy for Osteoarthritis

- Moseley et al. reported on a placebo-controlled trial of arthroscopic surgery for osteoarthritis of the knee involving 180 pts.
- Although the efficacy of this procedure had been suggested by non-placebo controlled studies, no benefit over placebo was shown in this well – designed study
- The authors calculated the cost of this intervention at $3.25 billion/year

Back to your Phase II trial

- To find out how effective transplantation of fetal dopamine neurons are for the treatment of Parkinson's disease, you decide that a placebo-controlled surgical trial is necessary

TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE PARKINSON'S DISEASE

CURT R. FREED, M.D., PAUL E. GREENE, M.D., ROBERT E. BREEZE, M.D., WEI-YANN TSAI, PH.D., WILLIAM DUMOUCHEL, PH.D., RICHARD KAO, SANDRA DILLON, R.N., HOWARD WINFIELD, R.N., SHARON CULVER, N.P., JOHN Q. TROJANOWSKI, M.D., PH.D., DAVID EIDELBERG, M.D., AND STANLEY FAHN, M.D.

- The first double-blind, sham-surgery-controlled trial of the implantation of embryonic dopamine neurons in patients with severe Parkinson's disease
- 40 patients (20 sham surgery controls), ages 34 – 75
- Primary outcome measure: a novel subjective global rating of clinical improvement or deterioration, scored by patients, at one year

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Protocol excerpts

- TRANSPLANT SUBJECTS: “4 twist-drill holes through the frontal bone were made along the planned axis of the tracks. The tissue implants were placed with the use of a stainless-steel guide. A volume of 20 uL, which was deposited continuously as the needle was withdrawn through the putamen. After a 2-min wait for the stabilization of pressure, the cannula was removed from the brain.”
- PLACEBO CONTROLS: “The patients in the sham-surgery group underwent an identical procedure except that the dura mater was not penetrated after the twist-drill holes had been made in the frontal bone. In an effort to maintain blinding, the patient was asked “Are you ready for the implant now?”

Results

- Unfortunately for the prospects of surgical grafting, the efficacy was found to be no better than sham procedure in 2 RCTs
- Significant placebo were detected
- Also of note: they unexpectedly detected a serious adverse reaction of graft-induced dyskinesias in many patients < 60yo.
- Conclusion: sham surgery controlled grafting trials prevented false positive conclusions and identified adverse reactions overlooked in uncontrolled surgical series

Major Criticism of Sham Surgery Controls

- Sham surgery designs produce “tension between the highest standard of research design and the highest standard of ethics.”

Response to criticism

- The problem is *not* tension between the highest standard of research design and the highest standard of ethics, but tension between obligations to individual research subjects and obligations to the larger group of pts and the general public

Proposed Criteria for Use of Sham Surgery Controls

- Given the necessity of minimizing risk to research subjects, sham surgery controls should not be the default method of constructing human clinical trials involving surgical interventions
- Sham surgery controls should be used only with careful justification
- These circumstances are likely to be rare

Albin R. *J Med Ethics.* 2002

Criteria For Use of Sham Surgery Controls

- General standards for ethical conduct of clinical research must be satisfied
- There cannot be reasonable alternative research designs
- There must be a procedure for minimizing the risk-benefit ratios
- The minimum # of subjects should be enrolled
- There should be a vigilant, independent safety monitoring board, including predefined stopping rules and unusually frequent oversight

The importance of understanding the "Why's" and "How's" of research

- Avoid the <u>therapeutic misconception</u> (confusion of research with individualized treatment)

- Understanding allows you to make a fully-informed decision that takes your motivations and goals into account

Questions to ask yourself when you consider participating in research

- What is your motivation to participate? (self-benefit, altruism, both)
- What is the goal of the study? (remember, Phase I trials test safety, Phase II trials test efficacy)
- Are you able to reconcile the answers to the above questions?