

Fetal Cell Transplantation For PD Trials with a Sham Neurosurgical Arm

C. Warren Olanow, MD, FRCPC
Professor of Neurology and Neuroscience
Chairman Emeritus, Department of Neurology
Mount Sinai School of Medicine
New York, NY

Conflict of Interest

- **Consultant**
 - Teva/Lundbeck
 - Novartis/Orion
 - Abbot/Solvay
 - Merck/Schering Plough
 - Ceregene
 - Pharm2B
 - GSK
- **Stock/Options**
 - Ceregene
 - Clintrex

Double Blind Sham-Controlled Trials of Dopaminergic Transplantation in PD

- Fetal nigral transplantation
 - Freed et al, NEJM
- Fetal nigral transplantation
 - Olanow et al, Ann Neurol
- Fetal porcine nigral transplantation
 - Unpublished
- Spheroids (retinal pigmented epithelial cells)
 - Unpublished

Open Label vs Double Blind Trials

Efficacy

	Open Label Trials
Fetal nigral (Freed)	Positive
Fetal nigral (Olanow)	Positive
Fetal porcine nigral	Positive
Spheramine	Positive

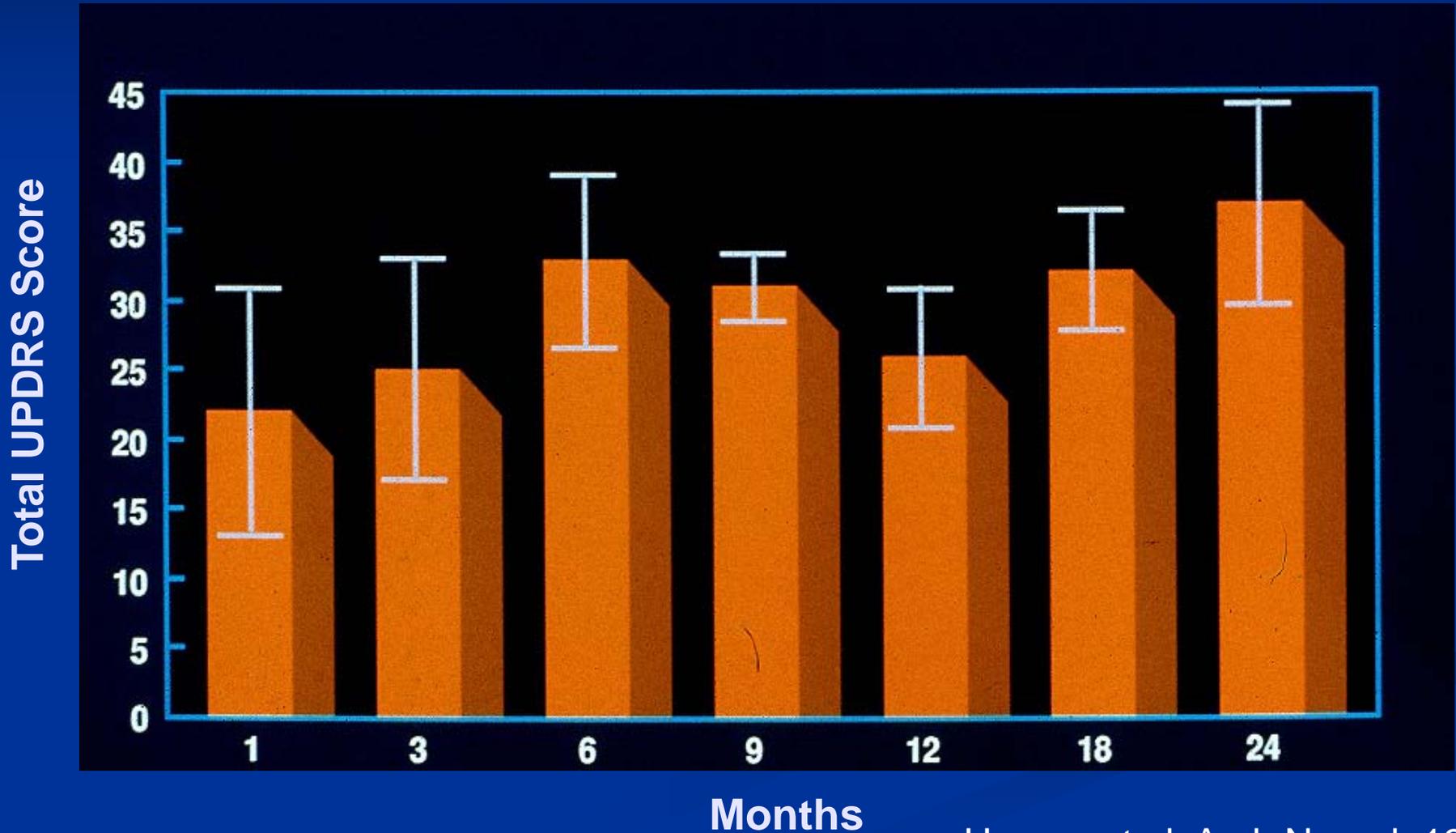
Open Label vs Double Blind Trials

Efficacy

	Open Label Trials	Double-Blind Trials
Fetal nigral (Freed)	Positive	Negative
Fetal nigral (Olanow)	Positive	Negative
Fetal porcine nigral	Positive	Negative
Spheramine	Positive	Negative

Fetal Nigral Transplant – Open Study

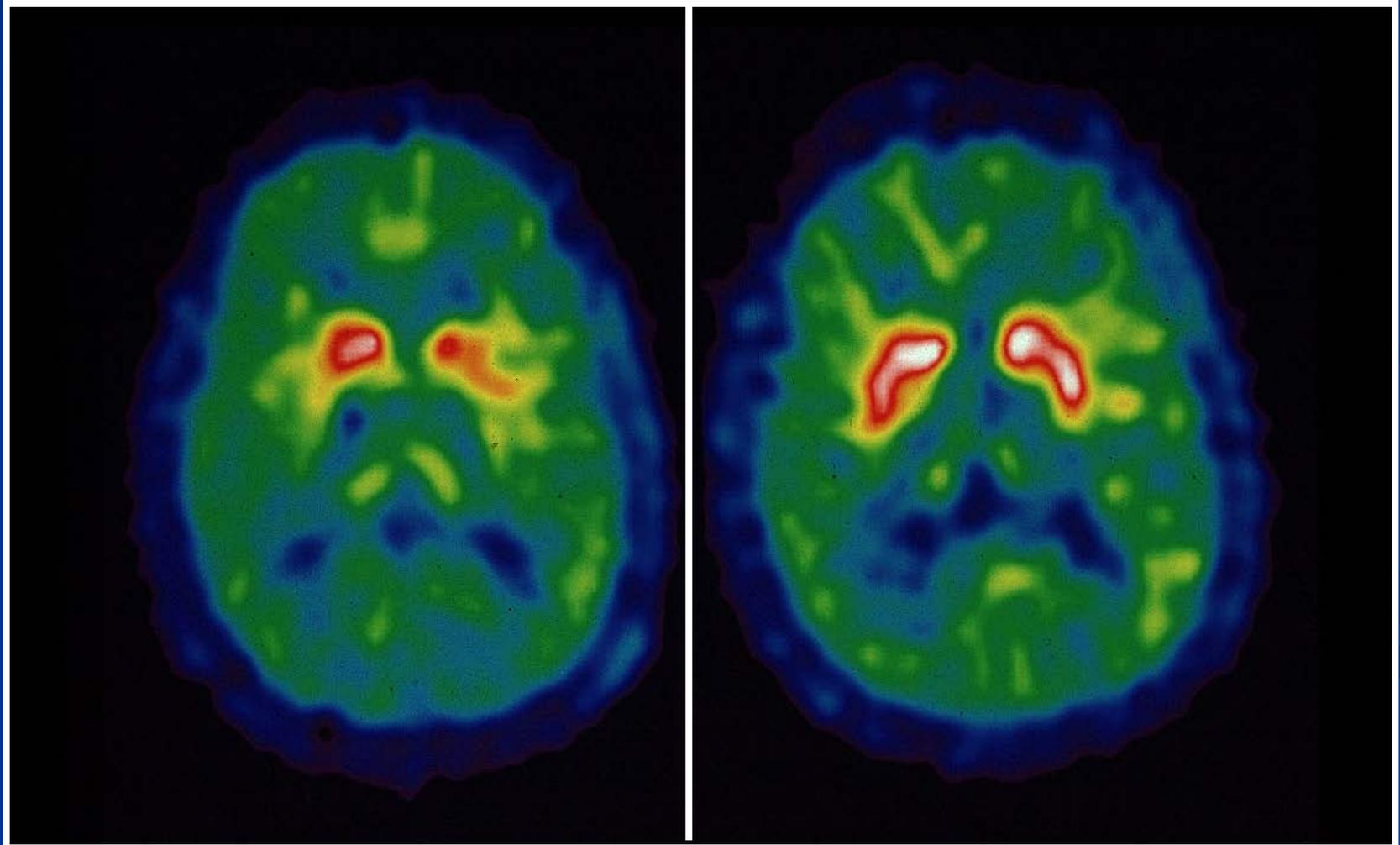
% Improvement in Total UPDRS “OFF”



Fetal Nigral Transplant Open Label Study FD-PET Studies

Pre-Transplant

Post-Transplant

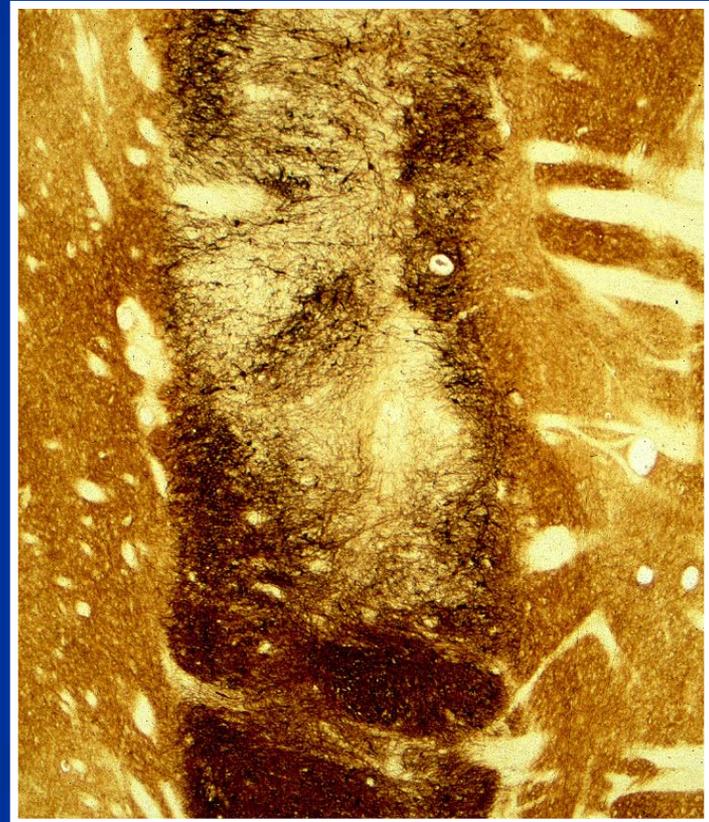


TH Staining of Transplanted and Non-Transplanted Regions of Striatum

Non-Transplanted Region

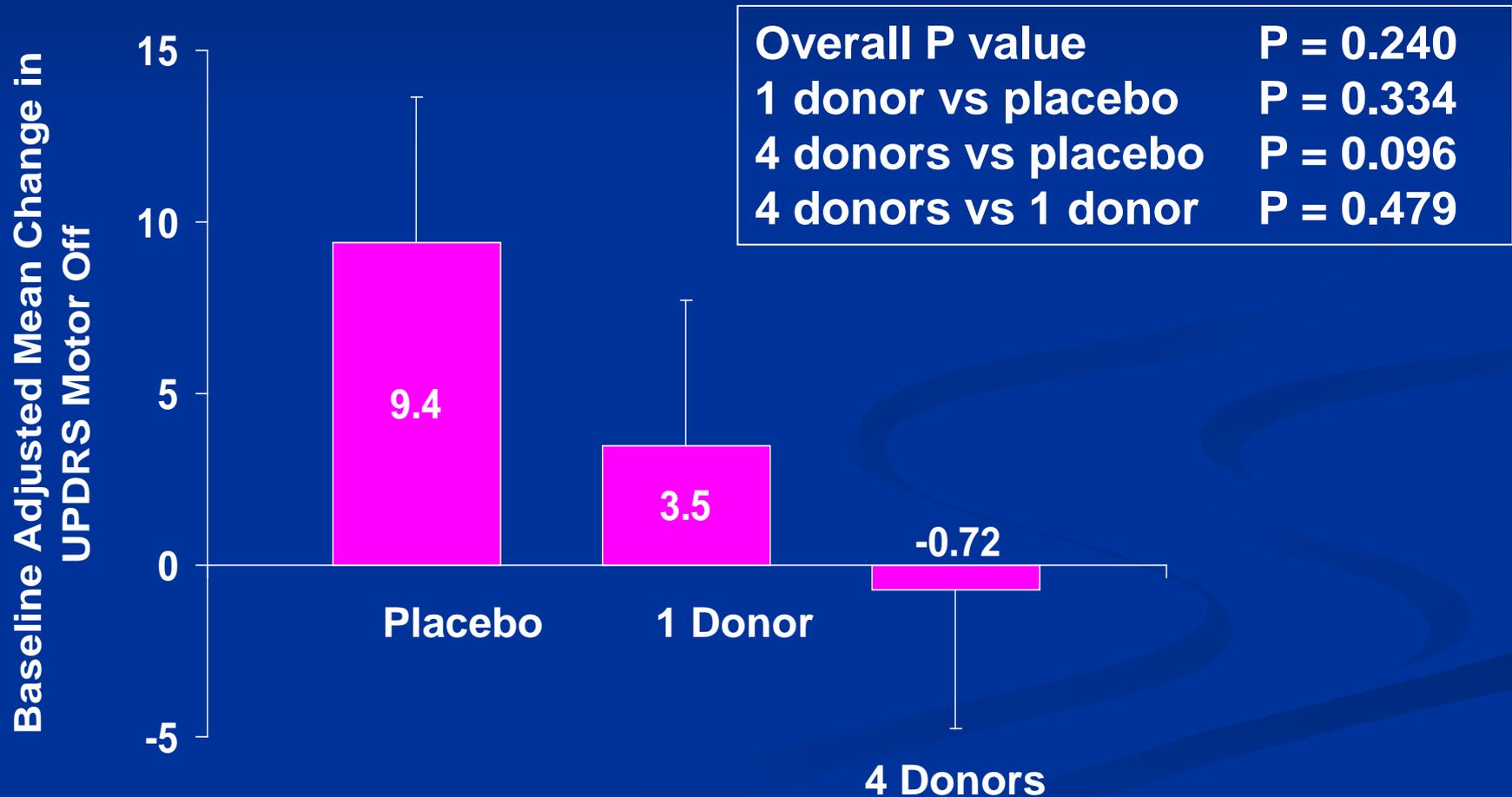


Transplanted Region



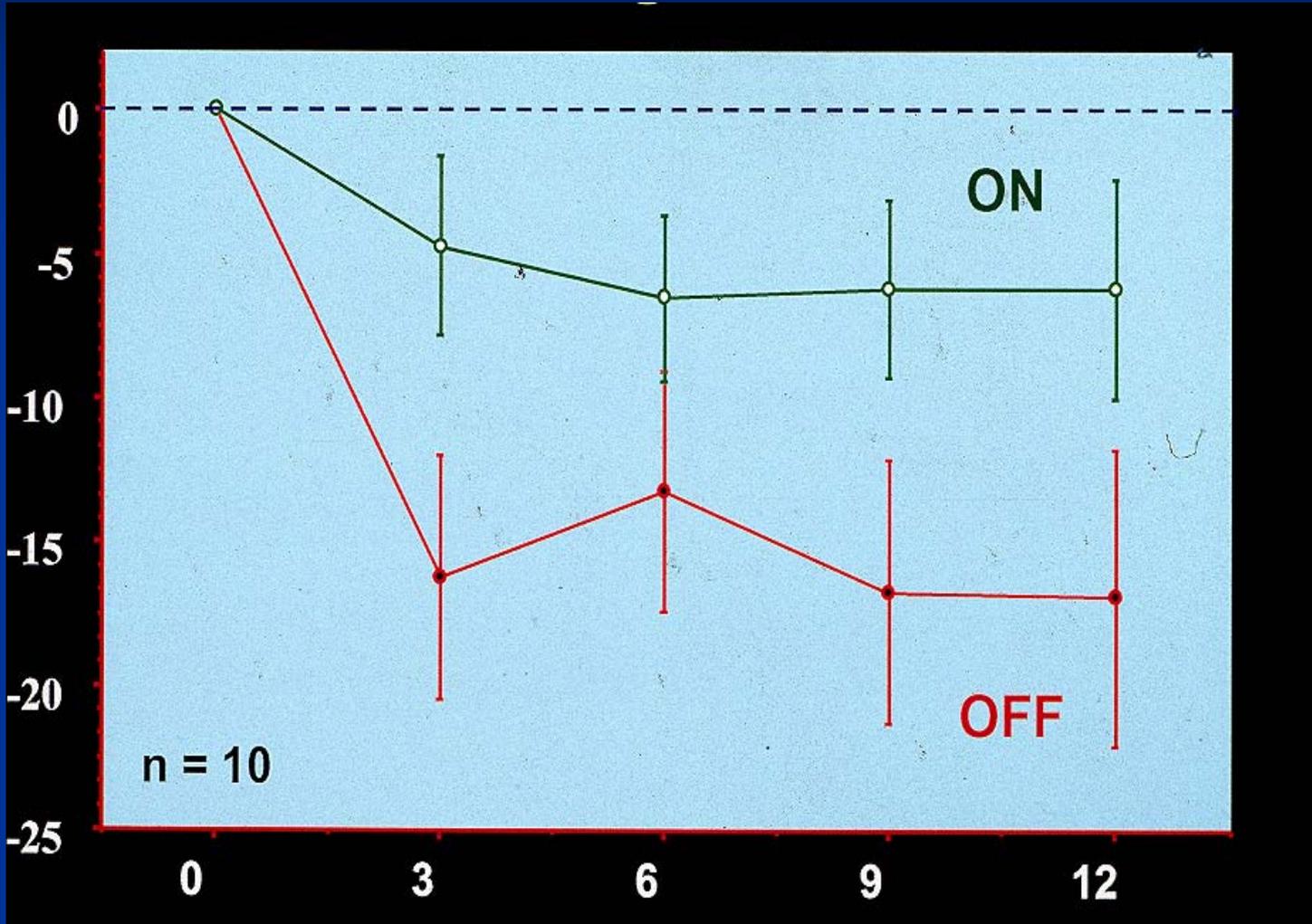
Fetal Nigral transplant Study

Δ UPDRS Motor Off \pm SE



Porcine Fetal Nigral Transplantation Open Label Trial

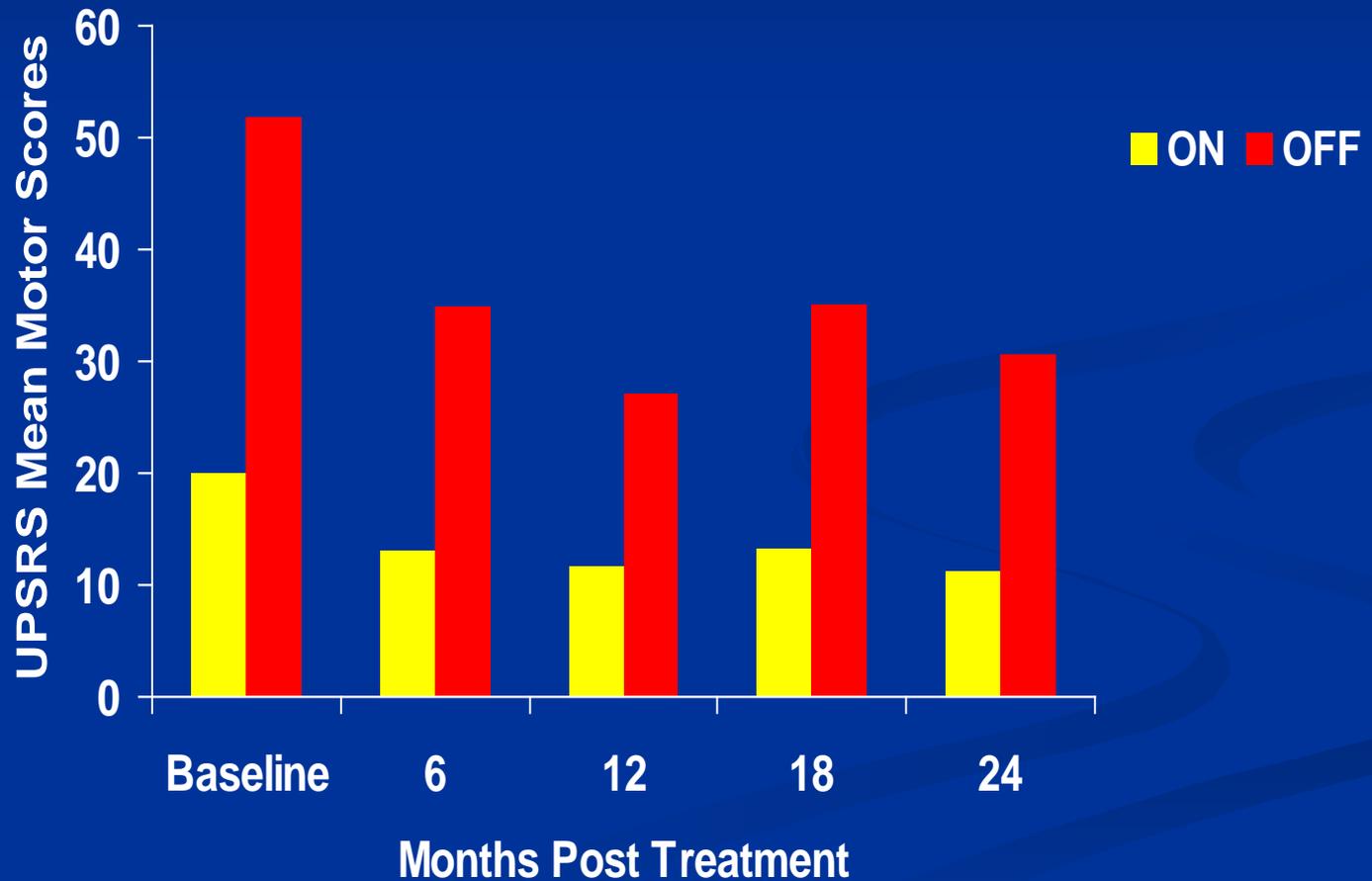
% Improvement in Total UPDRS Score



Months Post Transplant

Spheramine

Mean UPDRS Motor Scores



Open Label vs Double Blind Trials

Adverse Events

	Open Label Trials
Fetal nigral	
Off-med dyskinesia	Not Reported
Fetal nigral porcine	
Toxic encephalopathy	Not Reported
Spheramine	
Venous infarction	Not Reported

Open Label vs Double Blind Trials Adverse Events

	Open Label Trials	Double blind trials
Fetal nigral		
Off-med dyskinesia	Not Reported	Up to 56% of cases
Fetal nigral porcine		
Toxic encephalopathy	Not Reported	1 case
Spheramine		
Venous infarction	Not Reported	Multiple cases

Off-Medication Dyskinesia – Off State

34

24-month visit

OFF meds

NIH Specified Issues

- Factors We Considered in Deciding to Include a Placebo Arm
- Safety Assessments
- Ethical Considerations
- Would you design Trial Differently
- Did studies fail because of type II error



The **NEW ENGLAND**
JOURNAL of **MEDICINE**

**Use of placebo surgery in a controlled
trial of a cellular-based therapy for
Parkinson's disease**

**Freeman TB, Vawter DE, Leaverton PE, Godbold
JH, Hauser RA, Goetz CG, Olanow CW**

New Eng J Med 1999; 341: 988-992

Factors Considered in Inclusion of Placebo Arm

- Unreliability of open label studies
 - Placebo
 - Physician bias
- Feasibility of performing double blind, sham-controlled, surgical trials
 - Perform surgery at remote site
 - Script surgical procedure
 - Anesthesia for all patients
 - Partial thickness burr hole
 - Separate treating and evaluating investigators
 - Independent, neurology/neurosurgery team to manage complications

Factors to consider in double blind placebo controlled surgical trial

- Study must address an important question
- There must be evidence to suggest that the intervention is effective
- Risk:reward ratio must be acceptable
- Efforts should be made to minimize risks for sham-treated patients
- Procedures must be in place to "blind" both subjects and investigators
- Study design should be sufficiently rigorous to assure that it will answer the research question

Factors to consider in justifying double blind placebo controlled surgical trial

- Informed consent must be rigorously addressed
 - Informed consent should clearly identify all of the risks of participation in the study.
 - Subjects should fully understand the purpose, procedures, risks, and benefits of the trial, and must be advised of alternative therapies.
 - Informed consent must be approved by IRB and appropriate regulatory agencies
- Ethicist was active member of steering committee

How Did Sham Arm Help in Efficacy Assessments

- Demonstrated lack of efficacy of the transplant protocol that we employed
 - Suggested open label assessments compromised by effects of placebo and physician bias
- Without double blind studies, these procedure might now be widely performed based on the results of open label studies

How Did Sham Arm Help in Safety Assessments

- Identified adverse events not reported in open label trials
 - Fetal nigral transplant - Off medication Dyskinesia
 - Fetal porcine nigral transplant – toxic encephalopathy
 - Spheramine – venous infarction
- No clinically significant adverse events related to surgical or experimental intervention reported in placebo patients who underwent a sham-control procedure

Did studies fail because of Type II Error

- Type II error unlikely because, In comparison to Open label trials
 - Entry criteria were the same
 - Transplant protocol was the same
 - Variability at baseline was no greater
 - Sample size was larger

Future Phase II/III Transplant Trials

- Would use double blind sham-controlled trial
- Younger patients
- Milder patients
- Patients with relatively pure dopamine lesion – avoid patients with clinically significant non-dopaminergic problems (e.g. dementia and postural instability)
- Immunosuppression throughout duration of trial

Future Phase I Transplant Trials

- Larger sample size (approx 12)
- Staged recruitment (2 pts at a time)
- Randomized control group
 - Best medical treatment or DBS
- Blinded evaluators
 - Separate from treatment investigator
 - Gown patients to mask surgical procedure
 - Blinded randomized video assessment

The double-blind placebo controlled trial is the “gold standard” for the assessment of a new intervention

Physicians must demand the same high standards of science for new operations as we do for new medicines. The alternative is uncontrolled human experimentation...

David A. Grimes, 1993

The methods to assess surgical technologies are well accepted and widely available; what remains to be seen is whether we as a profession have the moral courage to use them.

David A. Grimes, 1993