

Parkinson's Disease Trials: A Critical Assessment

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Disclosures

Critical Assessment of Parkinson's Trials

None

Transplant trials

Widner Study

Critical Assessment of Parkinson's Trials

- Widner H, Tetrud J, Rehncrona S, Snow B, Brundin P, Gustavii B, Björklund A, Lindvall O, Langston JW. *Bilateral fetal mesencephalic grafting in two patients with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)*. N Engl J Med. 1992 Nov 26;327(22):1556-63.
- 2 case reports
- What is possible, not what is likely
- UCB for 0/2 safety events = 78%

Freed 1992 Study

Critical Assessment of Parkinson's Trials

- Freed CR, Breeze RE, Rosenberg NL, Schneck SA, Kriek E, Qi JX, Lone T, Zhang YB, Snyder JA, Wells TH, et al. *Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease*. N Engl J Med. 1992 Nov 26;327(22):1549-55.
- N=7
- Heterogeneous treatment and immuno-suppression
- No masking
- No control over selection bias
- Are such large apparent effects realistic?
- UCB for 0/7 safety events = 35%

Spencer Study

Critical Assessment of Parkinson's Trials

- Spencer DD, Robbins RJ, Naftolin F, Marek KL, Vollmer T, Leranath C, Roth RH, Price LH, Gjedde A, Bunney BS, et al. *Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease*. N Engl J Med. 1992 Nov 26;327(22):1541-8.
- N=4 highly selected patients
- Design presupposes a benefit, as the controls were delayed surgery
- No control over observer bias
- Treatment effects are magical because transplantation on one side resulted in improvements on the other side
- UCB on 0/4 safety events = 53%

Hauser Study

Critical Assessment of Parkinson's Trials

- Hauser RA, Freeman TB, Snow BJ, Nauert M, Gauger L, Kordower JH, Olanow CW. *Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease*. Arch Neurol. 1999 Feb;56(2):179-87.
- N=6, safety and efficacy
- Multiple clinical efficacy outcomes with significance test
- No confidence intervals
- No formal control over observer bias
- UCB on 0/6 safety events = 40%

Bundin Study

Critical Assessment of Parkinson's Trials

- Brundin P, Pogarell O, Hagell P, Piccini P, Widner H, Schrag A, Kupsch A, Crabb L, Odin P, Gustavii B, Björklund A, Brooks DJ, Marsden CD, Oertel WH, Quinn NP, Rehncrona S, Lindvall O. *Bilateral caudate and putamen grafts of embryonic mesencephalic tissue treated with lazarets in Parkinson's disease*. Brain. 2000 Jul;123 (Pt 7):1380-90.
- N=5
- Primary purpose was to evaluate tirilazad to prolong graft survival
- External control
- Multiple clinical efficacy outcomes
- No direct measure of graft survival
- UCB for 0/5 safety events = 45%

Freed 2001 Study

Critical Assessment of Parkinson's Trials

- Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S. *Transplantation of embryonic dopamine neurons for severe Parkinson's disease*. N Engl J Med. 2001 Mar 8;344(10):710-9.
- N=40 random treatment assignment with the supposition that therapy was effective (subjects were assured that they could receive transplantation later, helping to justify the sham surgery)
- Masked
- Post hoc recipient age stratification was presented as the primary outcome
- No overall effect
- How would transplanted cells know how old the new brain is?

Olanow Study

Critical Assessment of Parkinson's Trials

- Olanow CW, Goetz CG, Kordower JH, Stoessel AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB. *A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease.* Ann Neurol. 2003 Sep;54(3):403-14.
- N=34 randomized study with placebo control
- Masked
- No overall effect
- Post hoc severity stratification

Barker Study

Critical Assessment of Parkinson's Trials

- An open label study of fetal ventral mesencephalic transplants in patients with early PD with the prediction that consistent clinical efficacy can be shown using modifications of the procedure (Barker).
- N=20 (second trial maybe N=60)
- Primary objective is safety, no graft-induced dyskinesias
- No obvious control over selection or ascertainment bias
- No external or internal controls
- Labeled as “phase 1” without obvious dose question
- UCB for 0/20 safety events = 15%
- “To show efficacy on a range of motor, non-motor, and imaging (including PET) measures”
- “we know it works”

Growth factor trials

Nutt Study

Critical Assessment of Parkinson's Trials

- Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF; ICV GDNF Study Group (Implanted intracerebroventricular Glial cell line-derived neurotrophic factor) *Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.* Neurology. 2003 Jan 14;60(1):69-73.
- N=50 (5 or 6 per dose group)
- Masked, placebo controlled, random treatment assignment
- AEs observed, no clinical improvements, no dose effect
- UCB for 0/5 safety events = 45%
- UCB for 0/6 safety events = 39%
- UCB for 0/38 safety events = 8%

Gill Study

Critical Assessment of Parkinson's Trials

- Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P. *Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease*. Nat Med. 2003 May;9(5):589-95.
- N=5, “phase 1 safety”
- No apparent dose question
- Multiple clinical outcomes
- What was the primary outcome?
- No control over selection bias or observer bias
- UCB for 0/5 safety events = 45%

Patel Study

Critical Assessment of Parkinson's Trials

- Patel NK, Bunnage M, Plaha P, Svendsen CN, Heywood P, Gill SS. *Intrapatamenal infusion of glial cell line-derived neurotrophic factor in PD: a two-year outcome study*. Ann Neurol. 2005 Feb;57(2):298-302.
- N=5 “phase 1”
- No control over selection or observer bias
- Multiple clinical outcomes
- What was the primary outcome?
- UCB for 0/5 safety events = 45%

Slevin 2005 Study

Critical Assessment of Parkinson's Trials

- Slevin JT, Gerhardt GA, Smith CD, Gash DM, Kryscio R, Young B. *Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminial infusion of glial cell line-derived neurotrophic factor*. J Neurosurg. 2005 Feb;102(2):216-22.
- N=10, no bias control
- Primary outcome was safety
- Multiple clinical outcomes as secondary, but they were presented as primary
- UCB for 0/10 safety events = 26%

Chebrolu Study

Critical Assessment of Parkinson's Trials

- Chebrolu H, Slevin JT, Gash DA, Gerhardt GA, Young B, Given CA, Smith CD. *MRI volumetric and intensity analysis of the cerebellum in Parkinson's disease patients infused with glial-derived neurotrophic factor (GDNF)*. Exp Neurol. 2006 Apr;198(2):450-6.
- Assumption that the technical methods are reliable for “no detectable effect”
- Implicit safety surrogate, for which there can be none
- UCB for 0/10 safety signals = 26%

Lang Study

Critical Assessment of Parkinson's Trials

- Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, Brooks DJ, Hotton G, Moro E, Heywood P, Brodsky MA, Burchiel K, Kelly P, Dalvi A, Scott B, Stacy M, Turner D, Wooten VG, Elias WJ, Laws ER, Dhawan V, Stoessl AJ, Matcham J, Coffey RJ, Traub M. *Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease*. Ann Neurol. 2006 Mar;59(3):459-66. Erratum in: Ann Neurol. 2006 Dec;60(6):747.
- N=34, randomized
- “Designed to confirm” clinical benefit
- No effect on primary outcome
- Stimulated some discussion of post hoc power

Lang Study Power

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- Hutchinson et al. state “the [Lang et al.] study was incapable of saying anything meaningful about the effect of GDNF on Parkinson’s disease” based on various sorts of post hoc power calculations
- Hutchinson et al. apparently did not recognize the signature of a null treatment effect
- Post hoc power calculations are generally a useless exercise, but especially uninformative under the null !
- Luckily, Matcham et al. were there to explain using confidence intervals

Slevin 2007 Study

Critical Assessment of Parkinson's Trials

- Slevin JT, Gash DM, Smith CD, Gerhardt GA, Kryscio R, Chebrolu H, Walton A, Wagner R, Young AB. *Unilateral intraputamenal glial cell line-derived neurotrophic factor in patients with Parkinson disease: response to 1 year of treatment and 1 year of withdrawal.* J Neurosurg. 2007 Apr;106(4):614-20.
- N=10, 1 year follow-up after treatment discontinuation
- No control over selection bias or observer bias
- Multiple clinical outcomes in a small study
- UCB for 0/10 safety events = 26%
- Did they miss a chance to do a masked withdrawal?

Issues

Critical Assessment of Parkinson's Trials

- Publication bias
 - many more patients have been treated than reported in the literature.
 - two masked trials of transplantation remain unpublished
- The uncontrolled studies are dissimilar enough that I believe aggregating data or cross-study synthesis is infeasible.
- Bias cannot be corrected by larger sample size or additional uncontrolled trials.
- Double masked transplantation studies remain today as important landmarks in the history of clinical trials.

Themes

Critical Assessment of Parkinson's Trials

- There appears to be the typical inverse correlation between study rigor and enthusiasm for the results.
- The principle of reductionism is often overlooked, allowing small preliminary studies focused on safety and feasibility to make statements about longer range clinical outcomes.
- Trials are plagued by presupposition of benefit, lack of masking, and multiplicity. I suspect all these limitations and others were clearly evident in the study protocols. All the positive results appear to be placebo effects, bias, or type 1 errors.
- Where can we find the needed discipline and healthy skepticism?

Themes

Critical Assessment of Parkinson's Trials

- The first of these studies were published 18 years ago. They had substantial methodological shortcomings unnecessary for the day and not acceptable today.
- 18 years later we are still using the same study “designs” and analyses that have the potential to mislead.
- I would look to the community of senior neurological clinical scientists to ask
 - Where is peer review of study protocols?
 - What are the journal editorial staffs and reviewers thinking?
 - Shall we spend the next 18 years the same way?