Parkinson’s Disease Trials: A Critical Assessment

Sham Surgery Workshop
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None
Critical Assessment of Parkinson’s Trials

Transplant trials
Widner Study

Critical Assessment of Parkinson’s Trials


• 2 case reports
• What is possible, not what is likely
• UCB for 0/2 safety events = 78%

- 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%

• 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

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- 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

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- 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%

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

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- N=34 randomized study with placebo control
- Masked
- No overall effect
- Post hoc severity stratification
Barker Study
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• 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”
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Growth factor trials
Nutt Study

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- 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**

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- 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%

- 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
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- 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

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- 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

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- N=34, randomized
- “Designed to confirm” clinical benefit
- No effect on primary outcome
- Stimulated some discussion of post hoc power
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

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- 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?
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?
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• 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?