Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases:

Neurotrophic Factor Trials for Parkinson's Disease

Mark Stacy, MD

Professor of Medicine/Neurology

June 30, 2010

Stacy Conflict of Interest

- **Research Grants:** Ceregene, EMD/Serono, Neuraltus, Novartis, NIH, Parkinson Study Group
- **Educational Grants:** Allergan
- **Safety Monitoring Board:** Biogen-Idec, Neurologix
- **Consultant:** Allergan, Biogen, GE Imaging, Lundbeck, Osmotica, Synosia, Teva
- **Speaking Honoraria:** Allergan, Boerhinger-Ingelheim, GlaxoSmithKline, Teva

All Rights Reserved, Duke Medicine 2007

Neurotrophic Factor Trials for Parkinson's Disease

- Review Glial Derived Neurotrophic Factor Trials
  - **Placebo controlled intra-Ventricular Trial**
  - **University of Kentucky Trial**
  - **University of Bristol Trial**
  - **Placebo-controlled intra-Putamenal Trial**
- Questions
  - **What factors were considered regarding inclusion of a sham neurosurgical arm?**
  - **How did the sham neurosurgical arm assist in safety assessments?**
  - **What were the ethical considerations, and how did these impact the trial design?**
  - **Was the placebo response seen more in physician-rated assessments or patient self-assessments?**
  - **How can you ensure that a negative outcome from a placebo controlled trial is not a Type II error?**

All Rights Reserved, Duke Medicine 2007

Intraventricular GDNF

Multicenter, randomized, double-blind, placebo-controlled, sequential cohort study comparing monthly ICV administration of placebo and 25, 75, 150, 300, and 500 to 4,000 g of GDNF in 50 subjects with PD for 8 months.

- 12 subjects received placebo
- 38 subjects received GDNF

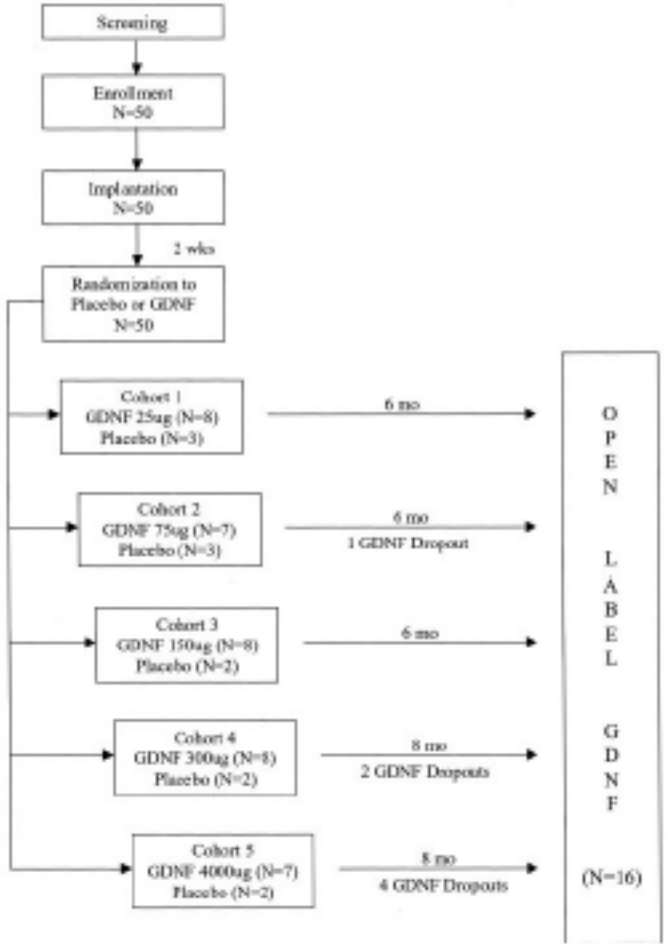
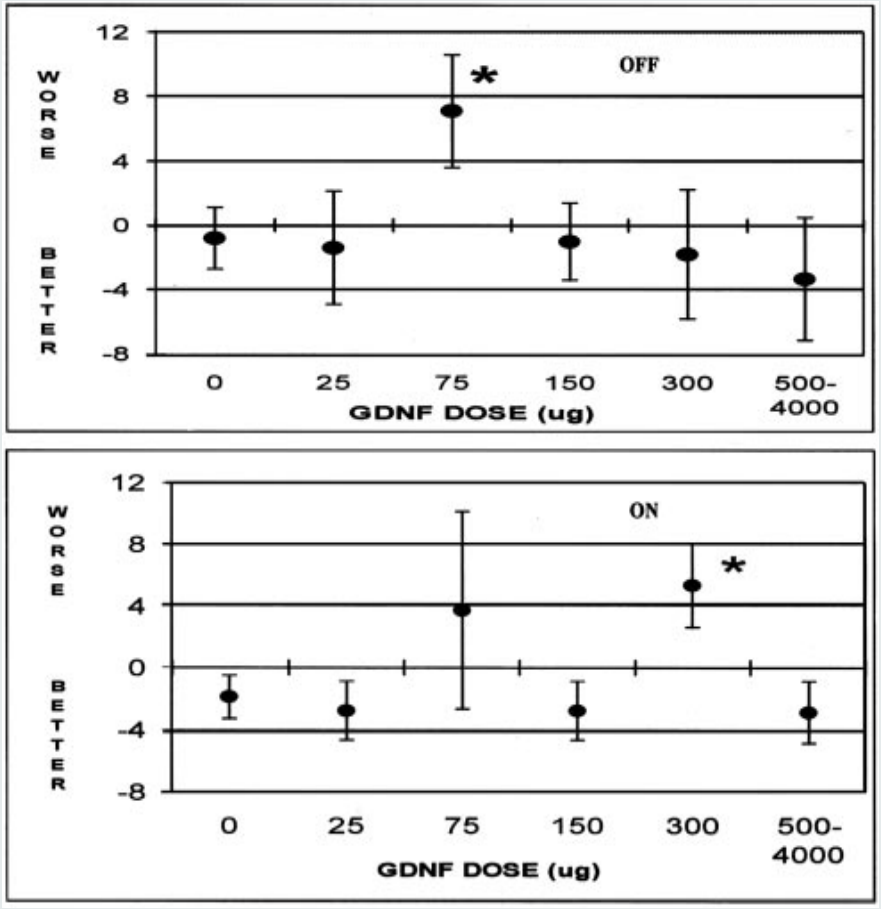


Figure 1. Flow of subjects through protocol. GDNF – glial cell line-derived neurotrophic factor.

Nutt JT et al. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 2003;60:69–73.

All Rights Reserved, Duke Medicine 2007

GDNF intraventricular dose response



- Total and motor UPDRS in the “on” and “off” states did change not at any dose
- Placebo and GDNF dose cohorts did not differ
- Changes in dopaminergic therapy from baseline to final observation did not differ
- The study had 80% power to detect a nine-point change in UPDRS off motor scores with eight subjects in a GDNF-treated group.

All Rights Reserved, Duke Medicine 2007

Adverse Events from iVe GDNF

Table 2 Adverse events occurring in more than 10% of GDNF-treated or placebo-treated subjects

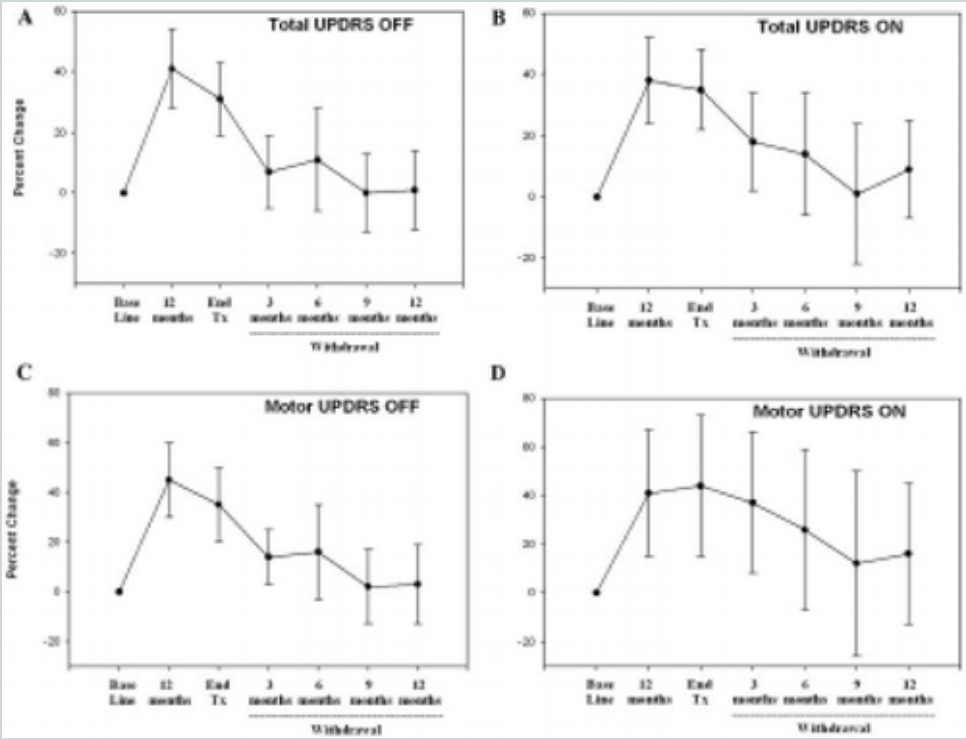
Adverse events	Placebo	GDNF
Gastrointestinal		
Nausea	25	87
Anorexia	0	55
Vomiting	8	40
Diarrhea	8	29
Weight loss	0	21
Dyspepsia	0	16
Sensory		
Paresthesias	8	82
Headache	25	71
Electric shock sensation	8	47
Dizziness	25	37
Arthralgias	25	16
Hypoesthesia	0	21
Vision abnormality	17	8
Tinnitus	17	0
Diplopia	0	16
Parasomia	0	16
Abdominal pain	0	13
Chest pain	0	13
Back pain	8	11
Limb pain	8	11
Taste perversion	0	11

	Placebo	GDNF
Parkinson-related		
Dyskinesia	33	42
Fatigue	17	40
Sudden "off"	8	26
Akinesia	25	18
Fall	0	21
Hypertonia	0	18
Hypokinesia	8	18
Asthenia	8	13
Dystonia	8	13
Tremor	8	13
Behavioral		
Depression	25	37
Insomnia	17	34
Hallucinations	25	18
Confusion	0	24
Anxiety	8	18
Abnormal dreams	17	11
Agitation	0	11
Autonomic		
Hypertension	25	5
Increased sweating	0	21
Constipation	17	3
Postural hypotension	8	13
General		
Injury	17	3
Rash	17	5
Respiratory congestion	8	11
Hyponatremia	0	11

Active subjects developed symptoms usually within days of infusion. No antibodies

All Rights Reserved, Duke Medicine 2007

GDNF Intraputamenal Open label trials



GDNF infused unilaterally into the putamen in 10 PD patients

UPDRS total scores after 1 year of therapy were improved by 42 and 38% in the off- and on-medication states.

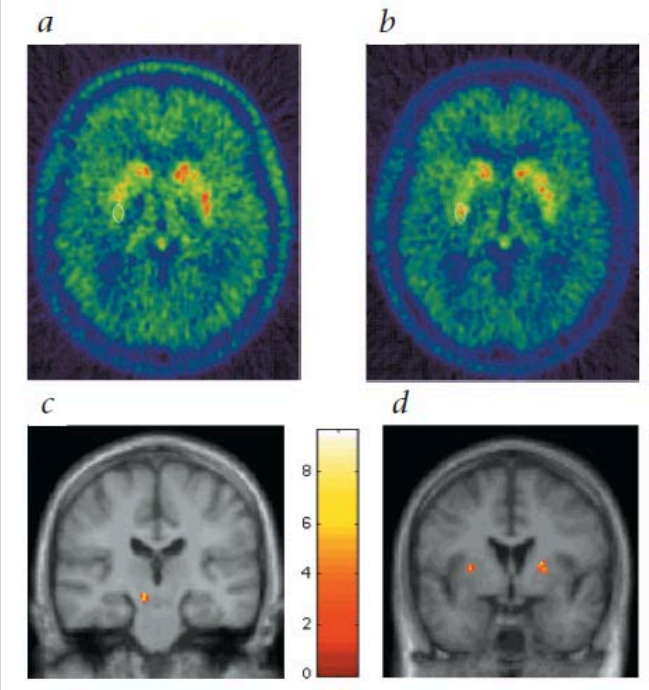
Benefits from treatment were lost by 9 to 12 months after the cessation of GDNF infusion.

One subject required explantation secondary to risk of infection. Seven (70%) patients developed antibodies to GDNF but without evident clinical sequelae.

Slevin JT et al. 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;106;614-20.

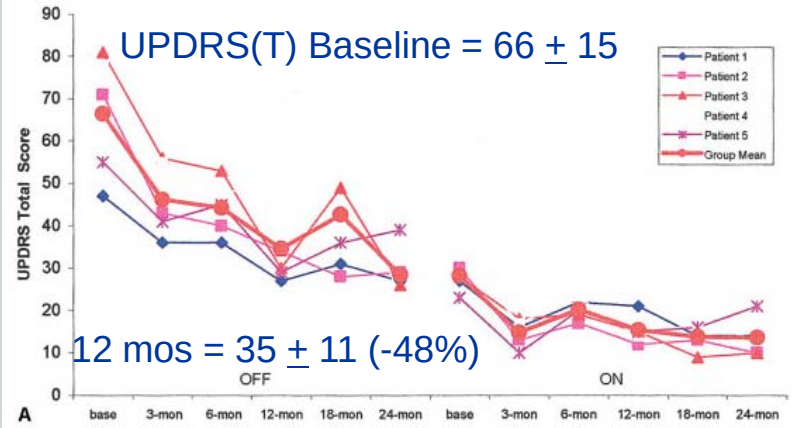
All Rights Reserved, Duke Medicine 2007

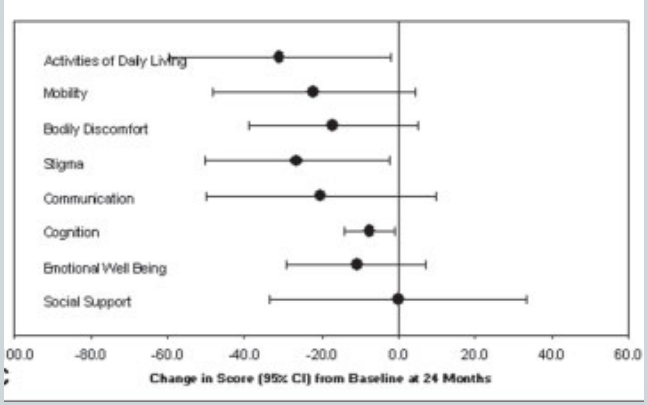
GDNF Intraputamenal Open label trials



[18F]dopa uptake at 6 months
R putamen = 17.9%
L putamen = 25.3%
R Substantia Nigra = 16.0%

GDNF infused unilaterally (1 subject) or bilaterally (4) into the putamen





PDQ-39

Gill SS et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 2003;9:589-95.
Patel NK et al. Intraputamenal infusion of glial cell line-derived neurotrophic factor in PD: a two-year outcome study Ann Neurol 2005;57:298-302

All Rights Reserved, Duke Medicine 2007

GDNF Intraputamenal Open label trials

Table 1 Patient data and overall effects of GDNF

	P1 (□)	P2 (△)	P3 (▽)	P4 (◇)	P5 (○)
Patient data					
Age (years)	62	46	56	56	51
Duration of Parkinson disease	6	13	30	27	19
Unilateral or bilateral pump (U/B)	U	B	B	B	B
L-dopa equivalents at 0 months	667	615	2154	680	762
Change in L-DOPA after 1 year	+10%	+6%	–54%	+17%	–40%
L-Dopa eq at 12 mos	734	652	991	796	457
Side effects					
Hypersalivation			*		*
Taste abnormalities	*		*	*	*
Lhermitte's	*	*	*	*	*
Headaches				*	*
Vivid dreams	*	*			
Apthous mouth ulceration			*	*	*
MRI changes	*	*	*	*	*
Nausea or vomiting					
Weight loss					
Pump-related discomfort					*
Procedural adverse events					
Repositioning of catheter	*				
Pump infection				*	
Other clinical effects					
Recovery of taste and smell	*			*	*
Revival of sexual function			*	*	*
Improved bladder function					*
Reduction in tinnitis					*

Increased T2 signal may only represent H_2O, the major component of the infusate.

Gill SS et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 2003;9:589-95.

All Rights Reserved, Duke Medicine 2007

Randomized Controlled Trial of Intraputamenal Glial Cell Line–Derived Neurotrophic Factor Infusion in Parkinson Disease

- Thirty-four PD participants randomized to receive bilateral continuous infusion of liatermin 15g/putamen/day or placebo.

- Primary end point: change in UPDRS motor score in the practically off condition at 6 months. Secondary end points included other UPDRS scores, motor tests, dyskinesia ratings, patient diaries, and 18F-dopa uptake.

- *Results: At 6 months, mean percentage changes in "off" UPDRS motor* score was not significant. *Secondary clinical end points were also similar*.
- 32.5% treatment difference favoring liatermin in mean 18F-dopa influx constant (*p 0.019) was observed.*

- It is uncertain whether technical differences between this trial and positive open-label studies contributed in any way this negative outcome.

Lang AE et al. Ann Neurol 2006;59:459–466

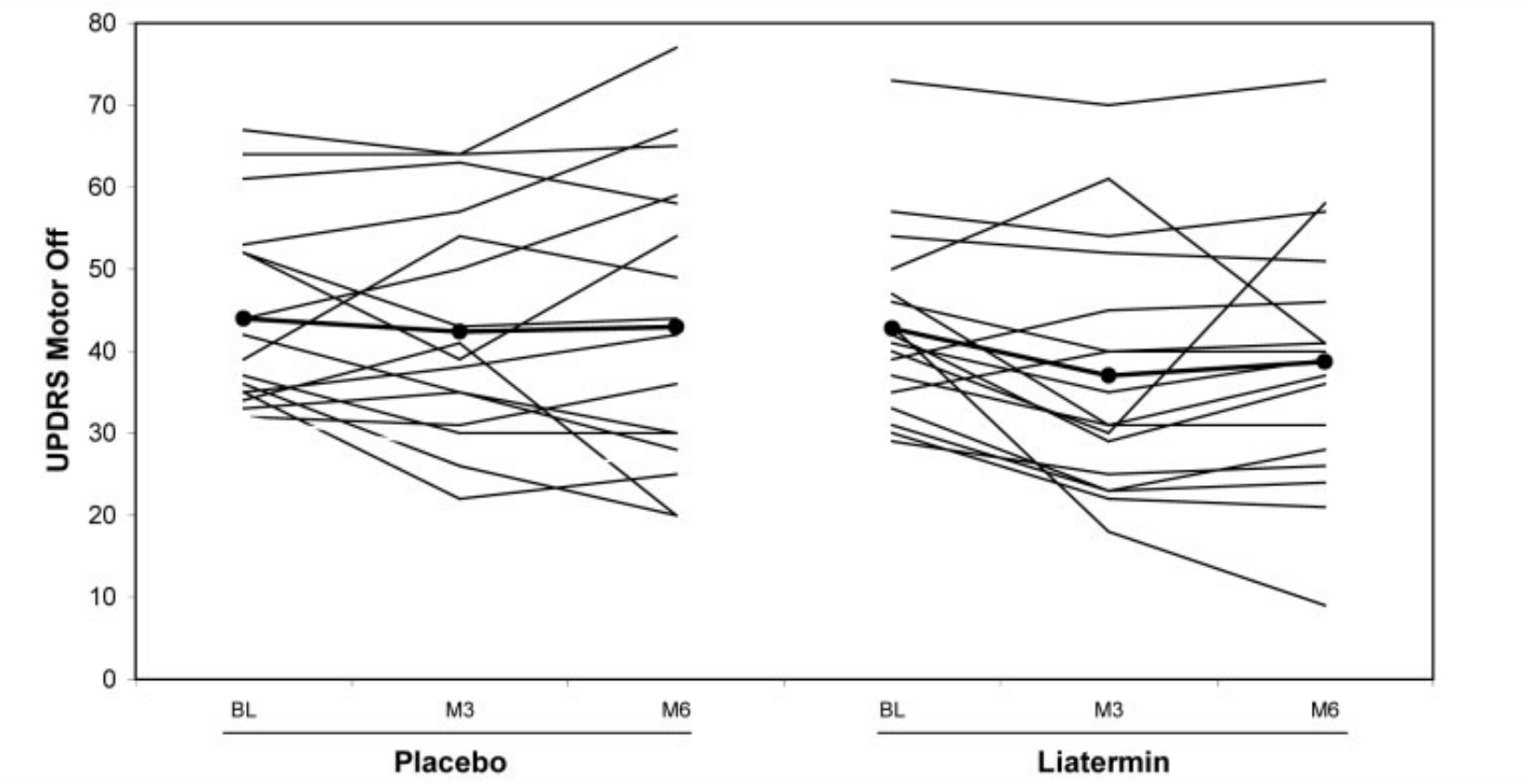
All Rights Reserved, Duke Medicine 2007

Secondary outcome variables: % change GDNF vs Placebo (*p*)

UPDRS I	85.3	(0.34)
UPDRS II (ADL)	16.8	(0.12)
UPDRS III	36.6	(0.097)
UPDRS IV	10.4	(0.67)
UPDRS Total	5.9	(0.47)
Timed walk	4.3	(0.83)
Purdue pegboard	9.4	(0.71)
L-Dopa dose	0.0	(0.92)
Off-time (hr/d)	0.6	(0.69)
On: no dyskinesia	**3.5**	**(0.008)**
On: mild dyskinesia	**2.8**	**(0.026)**
On: severe dyskinesia	**1.5**	**(0.012)**
Asleep	0.0	(0.92)

All Rights Reserved, Duke Medicine 2007

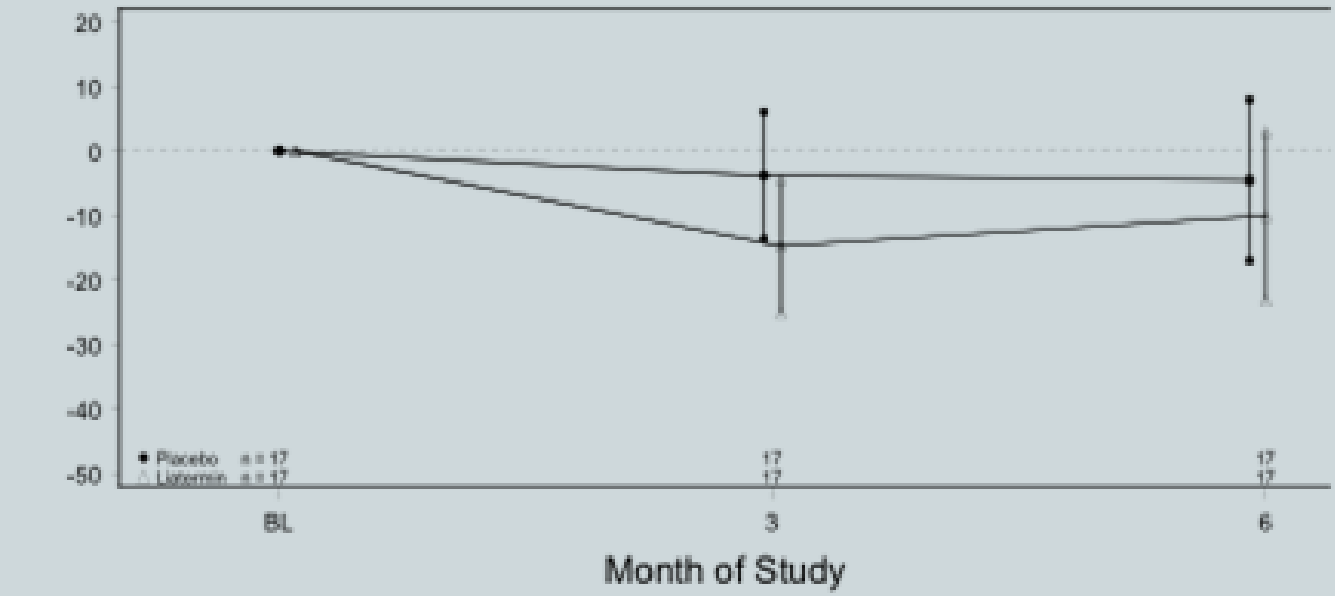
GDNF iPu Subject Response



There were no significant correlations between changes in UPDRS off motor score and 18F-dopa uptake

All Rights Reserved, Duke Medicine 2007

GDNF Percent Change in 'Off' UPDRS Motor Score



Missing Data at 3 and 6 months imputed by LOCF method

Placebo: -4.52 %

GDNF: -10.01%

Lang et al. Ann Neurol 2006

All Rights Reserved, Duke Medicine 2007

Adverse Events from iPu GDNF

Table 3. Adverse Events

Device-Related Serious Adverse Events[a]	Patients (N^b = 34)	Devices (N^c = 70)
N (%) with device-related serious adverse events	9 (26)	17 (24)
Catheter		
Misplacement/migration from Ipu target	2 (6)	3 (4)
Catheter tract		
Fluid collection	1 (3)	1 (1)
Pump		
Migration	2 (6)	4 (6)
Pump pocket		
Fluid collection	1 (3)	2 (3)
Hematoma	1 (3)	1 (1)
Infection	1 (3)	2 (3)
Surgery/anesthesia		
Intracranial hemorrhage	1 (3)	1 (1)
Other postoperative pain	1 (3)	2 (3)
Other		
Amnesia	1 (3)	2 (3)
Muscle spasms	1 (3)	1 (1)
Muscular weakness	2 (6)	4 (6)
Nausea	1 (3)	2 (3)
Partial seizures	1 (3)	2 (3)
Postprocedural hemorrhage (suture site)	1 (3)	1 (1)
Postoperative fever	1 (3)	2 (3)

Treatment-emergent adverse events[d]	Liatermin (N^b = 17)	Placebo (N^b = 17)
N (%) with treatment-emergent adverse events	17 (100)	11 (65)
Paraesthesia	11 (65)	3 (18)
Headache	5 (29)	1 (6)
Upper respiratory tract infection	4 (24)	1 (6)
Constipation	3 (18)	0 (0)
Dyskinesia	3 (18)	7 (41)
Insomnia	3 (18)	0 (0)
Dry mouth	2 (12)	0 (0)
Gastroenteritis viral	2 (12)	0 (0)
Hallucination	2 (12)	0 (0)
Lhermitte's sign	2 (12)	0 (0)
Migration of implant (infusion pump)	2 (12)	0 (0)
Postoperative wound complication	2 (12)	0 (0)
Parkinson's disease	1 (6)	3 (18)
Abnormal dreams	0 (0)	2 (12)
Postoperative infection	0 (0)	2 (12)
Urinary tract infection	0 (0)	2 (12)

Serious, device-related adverse events required surgical repositioning of catheters in two patients and removal of devices in another. Neutralizing anti-liatermin antibodies were detected in three subjects (one on-study and two in the open-label extension).

All Rights Reserved, Duke Medicine 2007

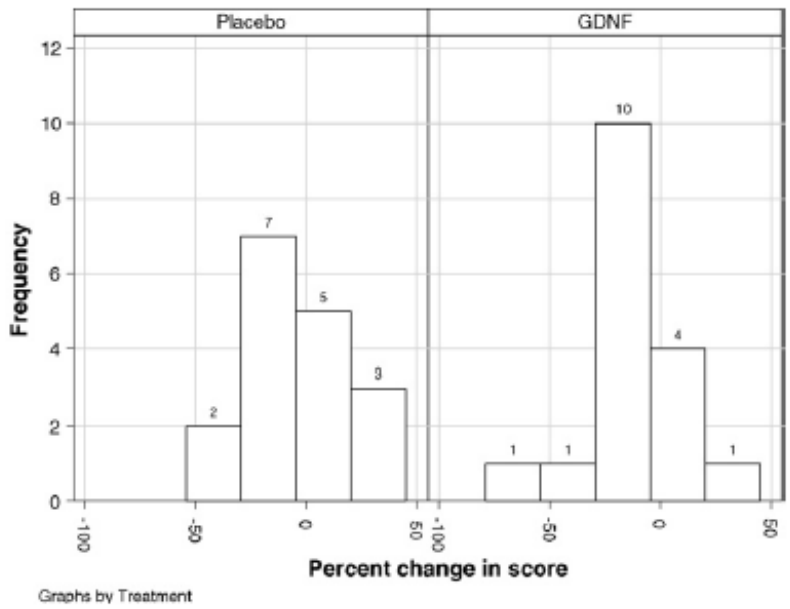
Short communication

GDNF in Parkinson disease: An object lesson in the tyranny of type II

Michael Hutchinson [a,*], Susan Gurney [b], Roger Newson [c]

[a] Department of Neurology, New York University School of Medicine, 400 E. 34th Street, Suite RR 311, New York, NY, USA
[b] Mailman School of Public Health, Department of Epidemiology, Columbia University, 722 W. 168th Street, New York, NY, USA
[c] Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College London, 47 Praed Street, London W1 1NR, UK

Received 28 April 2006; received in revised form 21 June 2006; accepted 22 June 2006



"In other words, it is possible just to *inspect the data and see that the study was underpowered."*

The main problems with the study...
1. The standard deviation was larger than anticipated
2. The study data do not meet normality criteria
3. The confidence interval for the median difference contains a broad range of between-treatment differences in disability score which might be considered clinically interesting…

"The real tyranny is in missing a slightly smaller, *but still very large, effect. For example, detection of a 20% or even a 15%* difference in means over a six month period would surely render GDNF the most important clinical neuroscientific discovery to date…rendering this study about as useful as guessing whether GDNF has a beneficial effect."

All Rights Reserved, Duke Medicine 2007

ELSEVIER

Journal of Neuroscience Methods 163 (2007) 193–196

www.elsevier.com/locate/jneumeth

Short communication

GDNF in Parkinson's disease: The perils of post-hoc power

James Matcham [a], Michael P. McDermott [b], Anthony E. Lang [c,*]

[a] *Amgen Ltd., Cambridge, United Kingdom*
[b] *Department of Biostatistics and Computational Biology, University of Rochester, USA*
[c] *Division of Neurology, University of Toronto, Canada*

Received 11 January 2007; received in revised form 2 April 2007; accepted 2 May 2007

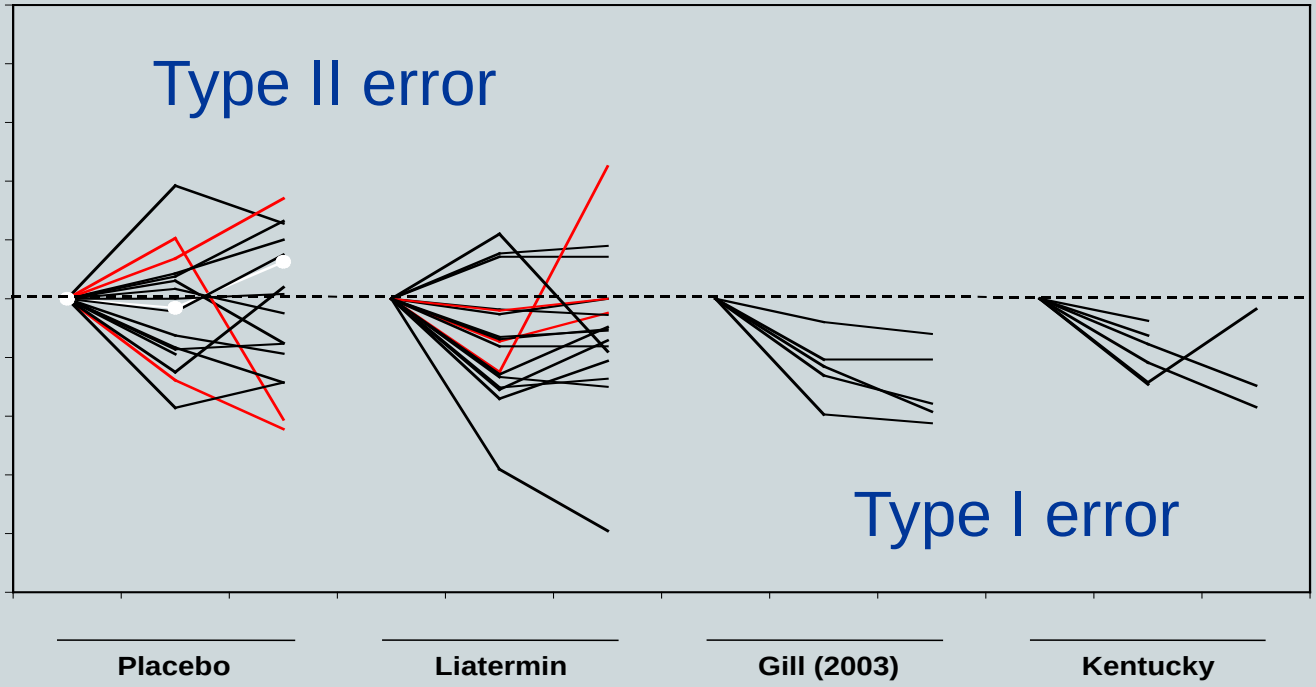
- "[Hutchinson et al] give detailed post-hoc power calculations assuming that the observed standard deviation from the double-blind trial is the true value, and conclude from these that the trial had insufficient power…

- The main philosophical objection to post-hoc power calculations is that power is a pre-experiment probability concerning a hypothetical result. Post-hoc power does not make proper use of the data that were actually observed concerning the magnitude of the treatment effect and its calculation is only performed after a "negative" result…

- There is general agreement that study reports should stress confidence intervals rather than p-values and current standards for the reporting of results of clinical trials appropriately adopt this philosophy… It is well documented that such calculations are unhelpful and potentially misleading and their routine use would represent a step backward in terms of the standards for the reporting of results of clinical trials."

All Rights Reserved, Duke Medicine 2007

GDNF Percent Change in 'Off' UPDRS Motor Score



All Rights Reserved, Duke Medicine 2007

Questions from the agenda

- What factors were considered regarding inclusion of a sham neurosurgical arm?
  - There was always to be a placebo arm in the original GDNF intraventricular infusion trial
  - In the initial trial design meeting for the iPu GDNF, there was at least unanimous assent for a placebo arm
- How did the sham neurosurgical arm assist in safety assessments?
  - Placebo subjects demonstrated fewer adverse events; these have not been assessed for statistical difference. However, no subject receiving only placebo is at risk for antibodies
- What were the ethical considerations, and how did these impact the trial design?
  - GDNF was a potential neuro-restorative therapy in PD
  - Surgical procedures and the medication are associated with potential for risk
  - Safety and Efficacy need to be established, and the double-blind, placebo-controlled trial is the gold standard method
    - Double blind treatment in this case required neurosurgery.
  - Subjects who received the sham surgery would be allowed to receive GDNF treatment at the study conclusion, if efficacy demonstrated

All Rights Reserved, Duke Medicine 2007

Questions from the agenda

- Was the placebo response seen more in physician-rated assessments or patient self-assessments?
  - No differences in any assessments, neither investigator-rated or participant-rated were seen in the controlled trials.
- How can you ensure that a negative outcome from a placebo controlled trial is not a Type II error (effective treatment appears ineffective)?
  - This study was powered, based on published data, to detect change in UPDRS off motor score after 6 months to be 29.9% (active) and 2.9% (placebo) with a SD=20%. A sample size of 15 patients per group provided a 90% power to detect a 25% difference between the groups a significance of 0.05. The trial enrolled 17 subjects in each arm.
  - Are open label studies are prone to Type I error: “ineffective intervention appears effective?”

All Rights Reserved, Duke Medicine 2007

Conclusions

- Placebo-controlled trials of bilateral GDNF infusions have not demonstrated differences between groups
  - Intraventricular infusion (38 active, 12 placebo)
  - Intraputamenal infusion (17 active, 17 placebo)
- Open label trials of unilateral GDNF infusions have produced encouraging results
  - University of Kentucky (10 subjects; 42% improvement Total UPDRS)
  - University of Bristol (5 subjects: 48%)
- Adverse events
  - (n=70 GDNF): 11 iPu subjects developed GDNF antibodies. GI symptoms, HA, sensory disturbances, hyponatremia more common than placebo. Much higher rate of AE in the controlled trial
  - (n=89 Surgery): catheter migration (3), device related infection (4)

All Rights Reserved, Duke Medicine 2007