Bioethics of Surgical Treatments for Neurodegenerative Diseases

Numan Ahmad, Farhan Ahmad
Joe R. & Teresa Lozano Long School of Medicine

ABSTRACT

Neurodegenerative disease (ND) continues to increase in incidence [1], as well as in prevalence coinciding with the growing aging population. Alzheimers and Parkinsons disease are the two most common NDs, affecting approximately 5 million and 500,000 Americans respectively. [2].

There is also a high attrition rate for clinical trials on NDs. In the years 2002 to 2012, the success rate for all Alzheimer's disease therapeutic clinical trials was 0.4% [3]. Similarly, in the case of Parkinson's disease, only 8% of pharmaceutical drugs passed Phase I safety and efficacy trials [4].

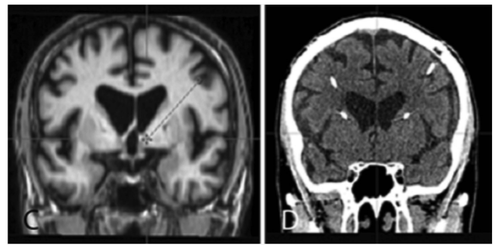
As the pathophysiology of NDs becomes better understood, a few surgical treatments have entered the clinical pipeline. Recently, at least one first-in-human (FIH) clinical trial has been conducted utilizing targeted, stereotactic neurosurgery to deliver nerve growth factor (NGF) to the basal forebrain of Alzheimer's patients, in an effort to slow cholinergic neuron degeneration [5].

Some surgical treatments for NDs have already shown promising results and have become part of treatment algorithms. [6] For example, the use of deep-brain stimulators in the subthalamic nucleus or globus pallidus interna for the treatment of refractory Parkinson's disease. Given these results, it is possible that surgical interventions for NDs may play a role in future curative efforts. Therefore, Institutional Review Boards may become more amenable to approving similar surgical clinical trials for NDs.

Neurodegeneration is well known for its presentation of distinct ethical challenges to providers, patients, and families. Surgical interventions add another layer of risks and complexity. The primary aim of this project is to analyze the ethical dimensions of future surgical interventions in the treatment of NDs—particularly Alzheimer's and Parkinson's disease. Comprehensive care for patients with NDs requires an honest discussion about bioethics that goes beyond the "four principles" model [7].

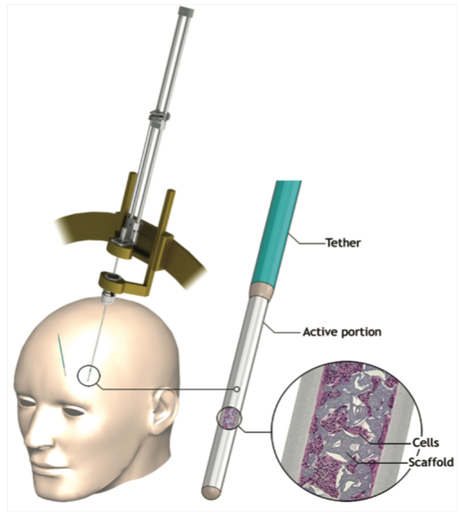
PRINCIPLES OF BIOETHICS

1. Autonomy
2. Beneficence
3. Nonmaleficence
4. Justice



PRACTICAL GOALS

1. Clear consent forms and policy for surrogate decision making
2. Disclosure and discussion preceding enrollment
3. Better translational models for surgically implanted devices
4. Developing stronger preclinical confidence-in-mechanism
5. Assessing the prospective enrollee's subjective state of mind



Wahlberg *et al.* 2012

Bioethical Concept	Practical Definitions	Socratic Questions
Informed Consent	Decisionally-capacitated consent after adequate information is provided and verifiably understood	●How do we accurately assess decision-making capacity in a patient with ND? ●When do we resort to surrogate decision makers to obtain consent? ●Should surrogate decision makers be allowed to provide consent for surgical trials?
Acceptable Risk	The level of psychosomatic injury and overall loss that can be tolerated	●What is the best way to explain risks in a manner that is understood by patients and decision makers? ●Is there an incongruence in the acceptable risk tolerance between patient and physician? How do we reconcile that incongruence and set reasonable expectations? ●What level of risk can be tolerated for surgical treatments of NDs? Should it be necessarily higher than non-surgical trials?
Placebo Surgery	A faked surgical intervention that omits any steps thought to be therapeutically necessary	●How important is procedural replication of the non-placebo surgery? ●Should particularly invasive clinical trials require placebo surgery? ●How do we disclose placebo surgery to patients without seeming disingenuous? ●How do we set expectations with patients enrolling in clinical trials with placebo surgeries? ●How do we maintain blindness on behalf of surgeons performing placebo surgeries?
Participant Selection	The process of selecting a representative group for trial enrollment, based on the population under study	●What patient population is best for Phase II efficacy trials? ○ How can we use the latest research to identify good candidates with generalizable criteria? ●Can rates of enrollment by surrogate decision makers compare to the rates of self-enrollment? ●How can we determine when it is or is not ethical to use a participant in a surgical clinical trial? ○ What factors might we consider? ● Given the slow progression of many NDs should we take personal lifestyle risk factors into account when selecting participants?
Personal Identity	Conscious awareness of oneself as distinct from other beings, and subsequently acting through self-determination	●At what point do implants, diseases, or mind-altering substances change one's sense of self? ●Is the diseased state the normal (natural) state with terminal illness? What if the patient has acclimated to his or her ND? ●Were we to find a way to restore lost memories or function, would the patient be the same person psychologically as they were prior to receiving treatment? ●Should surrogate decision makers be involved with decisions that impact identity and self-determination?
Biomedical Reductionism	A theoretical approach that seeks to explain all disease at the physical level as biologic processes	●Can NDs be reduced to multiple subtypes, each with a single etiology? ●Should surgical interventions be tailored to the patient at the expense of generic standardized trials? ●How can we use holism without resorting to a "one size fits all" approach to surgeries? ●How can we use personalized medicine (genes, biomarkers, epidemiologic criteria) while retaining justice for all patients with ND? ●Is there a place for palliative surgery, rather than curative surgery?

REFERENCES

1. Durães F, Pinto M, Sousa E. Old Drugs as New Treatments for Neurodegenerative Diseases. Pharmaceuticals (Basel). 2018;11(2)
2. Available at https://www.niehs.nih.gov/research/supported/health/neurodegenerative/index.cfm
3. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther. 2014;6(4):37.
4. Skibinski G, Finkbeiner S. Drug discovery in Parkinson's disease-Update and developments in the use of cellular models. Int J High Throughput Screen. 2011;2011(2):15-25.
5. Wahlberg LU, Lind G, Almqvist PM, et al. Targeted delivery of nerve growth factor via encapsulated cell biodelivery in Alzheimer disease: a technology platform for restorative neurosurgery. J Neurosurg. 2012;117(2):340-7.
6. Wagle shukla A, Okun MS. Surgical treatment of Parkinson's disease: patients, targets, devices, and approaches. Neurotherapeutics. 2014;11(1):47-59.
7. 7. Beauchamp, T. L., & Childress, J. F. Principles of biomedical ethics (6th ed.). New York: Oxford University Press; (2008)