Journal of Clinical Neuroscience 21 (2014) 1–5

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Ethical considerations in deep brain stimulation for psychiatric illness

Ryan A. Grant [a,*], Casey H. Halpern [b], Gordon H. Baltuch [b], John P. O'Reardon [c], Arthur Caplan [d]

[a] Department of Neurosurgery, Yale, New Haven Medical Center, 60 Temple Street, New Haven, CT 06510, USA
[b] Department of Neurosurgery, University of Pennsylvania Medical Center, Philadelphia, PA, USA
[c] Department of Psychiatry, University of Medicine and Dentistry of New Jersey, Stratford, NJ, USA
[d] Division of Bioethics, New York University, New York City, NY, USA

ARTICLE INFO

Article history:
Received 31 October 2012
Accepted 6 April 2013

Keywords:
Deep brain stimulation
Depression
Ethics
Mood
OCD
Psychiatric

ABSTRACT

Deep brain stimulation (DBS) is an efficacious surgical treatment for many conditions, including obsessive-compulsive disorder and treatment-resistant depression. DBS provides a unique opportunity to not only ameliorate disease but also to study mood, cognition, and behavioral effects in the brain. However, there are many ethical questions that must be fully addressed in designing clinical research trials. It is crucial to maintain sound ethical boundaries in this new era so as to permit the proper testing of the potential therapeutic role DBS may play in ameliorating these devastating and frequently treatment-refractory psychiatric disorders. In this review, we focus on the selection of patients for study, informed consent, clinical trial design, DBS in the pediatric population, concerns about intentionally or inadvertently altering an individual's personal identity, potential use of DBS for brain enhancement, direct modification of behavior through neuromodulation, and resource allocation.

1. Introduction

Deep brain stimulation (DBS) is an efficacious surgical treatment for many conditions.[1–3] It involves the implantation of electrodes into a particular region of the brain implicated in the pathophysiology of a neurologic or psychiatric disorder. Unlike its precursor ablative procedures, DBS has the benefit of being less destructive, reversible, and titratable to a patient's symptoms. DBS was approved by the US Food and Drug Administration (FDA) in 2001 for advanced Parkinson's disease (PD) and in 1997 for essential tremor (ET), and given its success in controlling many motor features of these conditions,[4] the application of DBS was extended to dystonia. More recently, there has been immense interest in the potential application of DBS to psychiatric disorders. For example, there are ongoing multi-institutional, randomized sham-controlled clinical trials of DBS of the ventral capsule/ventral striatum and subgenual cingulate (VC/VS) for treatment-resistant depression.[5,6] The VS, and particularly the nucleus accumbens, has been shown to respond abnormally to pleasurable stimuli in patients suffering from severe depression.[7] Using DBS in this region provided a 42% improvement in depression severity.[8] Similarly, patients who received DBS to the subcallosal cingulate gyrus[9,10] had an average response rate of 64.3%.[11]

Functional neuroimaging has implicated certain brain regions in the pathogenesis of treatment-resistant obsessive-compulsive disorder (OCD) and depression (TRD), with DBS demonstrating promise in both of these psychiatric disorders. A pilot study of DBS of VC/VS in 10 OCD patients, with long-term follow-up, reported a 36% decrease in disease severity and nearly a 50% improvement in global functioning.[12] This region of the brain has been consistently implicated in OCD,[12–14] which is not surprising given its central position between the amygdala, basal ganglia, thalamus, and prefrontal cortex – all regions known to be involved in this disorder.[15,16]

Despite these promising findings, some experts question whether there is currently enough preliminary evidence to warrant large-scale clinical trials. In a Consensus Conference examining the scientific and ethical issues in the application of DBS to affective disorders, some maintained that it is "premature to design large-scale randomized controlled trials of DBS for [affective disorders] before optimal targets and electrode settings have been determined in small, early-phase studies".[17] Nevertheless, positive outcomes from some pilot studies have led to the initiation of larger, randomized-controlled trials of DBS for mood disorders, which show encouraging results or are without adverse events for both depression and OCD.[18–20] The recent limited FDA approval, a Humanitarian Device Exemption, of DBS for OCD[21] provides further support for the future of broader testing of the feasibility, safety, and efficacy of DBS for neuropsychiatric conditions.

The explosion of new technology in the modern era has contributed to the birth of the subspecialty in bioethics known as neuroethics. This field encompasses the professional and procedural ethics of conducting neuroscience research, the manner in which

* Corresponding author. Tel.: +1 248 761 4683.
E-mail address: ryan.grant@yale.edu (R.A. Grant).

0967-5868/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jocn.2013.04.004

such research is presented for application in treatment, the neurobiological basis of normative systems and feelings including spiritual and religious thoughts, the diagnosis of mental illness and mental proclivities, and lastly, the social implications of the outcomes of new neurological knowledge.[22–28] Given that the treatment of mood disorders with DBS remains investigational, it merits discussion as a part of neuroethics. We focus on the selection of patients for study, informed consent, clinical trial design, DBS in the pediatric population, concerns about intentionally or inadvertently altering an individual's personal identity, potential use of DBS for brain enhancement, direct modification of behavior through neuromodulation, and resource allocation.

2. Selection of potential patients

Selecting appropriate surgical candidates for DBS through patient eligibility criteria is of fundamental importance both in optimizing efficacy and safety. Yet, presently there are no standardized criteria for choosing appropriate candidates. Given the troubled history of psychosurgery based on anecdotal claims of efficacy,[29–33] research must proceed with great caution. Selection criteria must identify appropriate candidates who are physically, emotionally, and cognitively capable of both understanding and undergoing surgery as part of a trial. The patients ought to have a stable social environment and the availability of a family member or partner who can assist them in the participation in an early trial.

Since DBS in these subjects remains a non-standard therapeutic method, such applications remain experimental, necessitating protection of this vulnerable population through respect of fundamental ethical principles: respect for autonomy; justice in the selection of patients; competency of the investigators; adequate peer review; and non-malfeasance. Poorly selected patients may face risk from DBS especially if procedures are conducted by unqualified researchers, using invalid protocols with little systematic follow-up. Protocols that select individuals for these research trials based on factors known to contribute to maximal clinical outcome are paramount, as candidates for neural implants typically have severe disease and comorbidities such as personality disorders, which may predict suboptimal responses.[34] Recommendations have been developed by various consortiums in regards to protecting and selecting patients.[35,36] These include meticulous screening, consultation with ethicists and psychologists, excellence in surgery, evaluations using standardized rating scales, complete and uniform documentation, as well as comprehensive pre- and postoperative assessments by a multidisciplinary team[37] – consisting of neurologists, neurosurgeons, psychiatrists, ethicists, and nurses – in order to establish sound and best practice guidelines, especially regarding the ethical concerns of innovative practice. In summation, there may need to be an independent panel to assess these unifying but sometimes competing principles.

There are presently no clear-cut algorithms to select candidate patients for these trials. Nevertheless, generating such selection criteria must be overseen by an Institutional Review Board (IRB). It is reasonable for investigators to contact their IRB to work with them in developing strategies for patient recruitment and consent, keeping in line with the remit for safety. Prospective patients must demonstrate an ability to consent to participation in a research trial and have documented severe, functional impairment refractory to medical treatment. Additionally, all potential patients should receive a thorough neuropsychological examination because it may reveal cognitive deficits or other psychiatric comorbidities[38] that would preclude them from enrollment.[39,40]

Other selection considerations include social support, family commitment, and individual expectations. The expectations of individuals included in research trials, and by extension their families, will have to be kept realistic. Since one of the purposes of these trials is to test efficacy, patients need to be aware that there is a certain possibility of failure, potential adverse effects that may or may not be predicted, and a very unclear understanding of the chance for success.[41] If the patient expects remission of illness in the context of a trial and instead is either a partial or non-responder, the resulting disappointment may be potentially harmful. Thus, it is imperative to stress to potential patients the need to determine safety and to answer fundamental questions regarding the procedure.[42] Regardless, it has been documented that even well-screened individuals with alleviation of symptoms can still be disappointed secondary to a failure to reach a "perfect outcome".[41] Continuing social support and psychotherapy are important because it may be essential that families dedicate large amounts of time and energy in terms of preoperative and postoperative care, access to care and the clinical research center, screening appointments, device programming and interrogation, medical management, and continued follow-up throughout a trial.

3. Informed consent

Informed consent is a process of communication between a physician and a patient, or the authorized surrogate, resulting in an understanding of the risks and benefits of a research trial particularly in the context of a surgical intervention.[43] Informed consent can be challenging in psychiatric disorders,[44] but there is evidence that as a whole, patients with treatment-refractory clinical depression or OCD are similar to other patients with severe, chronic medical diseases with regard to the capacity to consent.[45–47] A clinical diagnosis does not imply decisional incapacity nor should it rule such capacity out, as many patients demonstrate retained abilities to understand risks, benefits, and potential complications.[44,48] Furthermore, for those with reduced capacity, the decision-making abilities can be compensated by more intensive educational interventions[49] and the use of quizzes to help establish comprehension. Regardless, secondary to past abuses of psychosurgery, informed consent of these individuals must be scrupulously safeguarded, with stringent and transparent patient selection as well as inclusion and exclusion criteria as described above. Furthermore, because DBS is often a last-resort procedure, patients and caregivers develop significant anxiety when discussing the operation, and they may rush the consent process and be willing to consent without being provided an adequate amount of information about the risks of surgery.[50] The investigational nature of these trials needs to be thoroughly explained to these patients and their families, who may be "prepared to risk everything" in hopes for a "cure".[42,51]

The inherent risks associated with DBS emphasize the need to establish adequate informed consent. Even though DBS does not require destructive brain lesions, which in itself decreases the risk of permanent postoperative neurological deficit,[52] there still is a significant incidence of adverse events associated with DBS in general. The complication rates for movement disorders can exceed 25%, however, recent meta-analytic work revealed that complications occur at a mean rate of 19% with a minimal overall impact on quality of life.[53–55] Overall, adverse effects secondary to DBS tend to be transient.[3] Moreover, the complication rate of DBS in psychiatric disorders is unknown, and stimulating reward-related regions in the brain may have serious side effects such as mania.[56,57]

Regarding informed consent, long-term care must also be understood, including the need for pulse generator replacement, as often as 6 months, until improved devices with greater longevity are developed.[58] Long-term complications are also possible, including infection, erosion, loss of effect, intermittent stimulation,