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Scientific and Ethical Issues Related to Deep Brain Stimulation for Disorders of Mood, Behavior and Thought

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Abstract

A two-day consensus conference was held in order to examine scientific and ethical issues in the application of deep brain stimulation in the treatment of mood and behavioral disorders such as major depression, obsessive-compulsive disorder, and Tourette syndrome. The primary objectives of the conference were to 1) establish consensus among participants about the design of future clinical trials of DBS for disorders of mood, behavior and thought and 2) develop standards for the protection of human subjects participating in such studies. Conference participants identified 16 key points for guiding research in this growing field.

Introduction

A National Institutes of Health and Dana Foundation–sponsored consensus conference, “Deep Brain Stimulation for Disorders of Mood, Behavior and Thought: Scientific and Ethical

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Issues," which was held in autumn 2007, explored concerns relating to the study of deep brain stimulation (DBS) as a potential treatment for disorders of mood, behavior and thought (MBT). The agenda combined brief presentations with extensive periods of open discussion. The participants included leading clinical investigators from different centers in the US and Europe, bioethicists, patient advocates, research policymakers, psychiatrists, neurologists, and other experts.

The stated aims of this meeting were: 1) to establish consensus among participants about the design of future clinical trials of DBS for disorders of MBT, including inclusion criteria and whether randomized, controlled trials should be required; and 2) to develop standards for the protection of human subjects who participate in such studies. Conference participants developed consensus on 16 statements regarding DBS as an experimental treatment for severe psychiatric illness. The meeting was recorded and transcribed, a manuscript drafted, and all participants were given the opportunity to contribute to several rounds of revision. The consensus items are given below, accompanied by brief summaries of the presentations and discussions that led to their formulation.

1. Continued research in deep brain stimulation (DBS) for disorders of mood, behavior, and thought (MBT) is supported by 1) evidence of changes in mood, affect and behavioral symptoms in patients undergoing DBS for the treatment of movement disorders and 2) by early reports of positive DBS outcomes in a small number of research subjects with depression, OCD and Tourette syndrome.

   Eleven of 37 studies (30%) reporting on mood change after DBS for Parkinson disease (PD) reported a significant improvement[1]. In nine studies that evaluated obsessive-compulsive symptoms in patients with PD, two reported a significant improvement and six report non-significant improvement following DBS[1]. Although these studies were not designed or powered to study mood and behavior changes as a primary outcome, they do provide evidence for investigating DBS as a treatment for depression, obsessive-compulsive disorder (OCD), and other disorders of MBT.

   Despite the strong interest in DBS for psychiatric disorders[2-4], the published experience is small. For OCD, the first report was in 2003[5]; a subsequent paper described 10 patients[6]. Unpublished data presented at the conference suggested that approximately 100 individuals with treatment-resistant OCD have had DBS surgery. However, different groups have used different neuroanatomical targets for stimulation, limiting comparability. A recently published subset of these data (N=26), however, does allow for comparison[7]. For depression, Mayberg and colleagues have described 20 patients[8,9], and three patients were reported by Schlaepfer *et al.*[10]. For Tourette syndrome, over 30 cases have been reported[11-14].

   One challenge facing the use of DBS for MBT is the identification of the appropriate anatomic site for stimulation. For PD, a primate model (MPTP-treated animals) identified increased excitatory activity in the subthalamic nucleus and the internal and external pallidum[15-18] suggesting it as a stimulation target. Animal models for disorders of MBT are limited. However, site selection for DBS based on an animal model of OCD has been reported[19]. In addition, while animal models have many advantages in identifying relevant neural circuitry, they are also imperfect and will need to be supplemented with data from other methodologies. Accordingly, functional neuroimaging of humans with major depression played a critical role in identifying putative stimulation sites for depression[20]. Conference participants felt there was a need for more basic research to support site selection for DBS of MBT.

2. DBS for disorders of MBT is at an early proof-of-principle stage and must be considered investigational. Currently, no single target has been validated or

demonstrated to be superior to others in any disorder of MBT. Therefore, it is premature to rule out the study of new implantation sites that have a good scientific rationale. The full range of risks and benefits need to be studied in patients with disorders of MBT.

The anatomic circuitry for disorders of MBT is complex. In the subthalamic nucleus, for example, the limbic, cognitive, and motor areas are not readily distinguishable, which may explain the affective changes seen with DBS for movement disorders. Likewise, fibers in the internal capsule follow a complex and convoluted course, suggesting that the specific fibers stimulated will depend on electrode placement and stimulation parameters (preliminary data, SNH). The pallidum is a structure with lengthy dendrites that receive input from multiple regions, which suggests that electrode placement will have different effects in different people due to inter-individual structural variation. The subthalamic nucleus is also a highly complex structure, and it is unknown whether DBS effects are achieved through stimulation of white matter tracts, neuron cell bodies or both.

If the hypothesis that many movement disorders are “circuit disorders” that result from pathologic disturbances in neuronal activity along specific neuronal loops is correct, then interventions at multiple sites along the circuit may be equally or differentially efficacious and may have different side effects[15]. In addition, the majority of current DBS targets for MBT disorders have already been lesioning targets. However, as neurocircuitry models of MBT disorders evolve, new DBS targets that have never been lesioning targets may emerge (e.g.,[8]). Conference participants concluded that researchers should avoid premature conclusions about optimal targets. Investigating alternative targets will enable investigators to determine which anatomic sites are more easily and reproducibly targeted and whether some sites have a lower incidence of operative risk or adverse events. Several participants felt that it would be premature to design large-scale randomized controlled trials of DBS for disorders of MBT before optimal targets and electrode settings have been determined in small, early-phase studies.

Surgical implantation of DBS systems is invasive and thus not a minimal risk procedure: infection, hemorrhage, and other common surgical complications are reported[1]. Operative risks are likely greater in more vascular regions. However, operative risks of DBS at *any* location are significant, and therefore careful consideration of potential adverse effects is critical when contemplating DBS. Furthermore, stimulation-dependent adverse effects including facial contractions, facial paresthesias, olfactory phenomena, anxiety, and mood fluctuations have been reported for some sites[6]. These effects tend to occur at higher levels of stimulation and may be avoidable or minimized by optimal targeting.

3. The comparative efficacy and safety of DBS versus other treatments, including ablative surgery, should be studied further. Such studies are ethical and scientifically necessary.

Available data suggest that the results of DBS and ablation of the subthalamic nucleus and internal pallidum in patients with PD are comparable. In OCD, published and unpublished data (Gabriëls and colleagues;[21]) suggest that capsulotomy can produce equivalent results to DBS of the internal capsule. One case has been reported of DBS following ablative cingulotomy in a patient with treatment resistant depression[22]. Comparative studies may be more complex ethically in cases where the DBS target region has never been a lesioning target. For target regions with existing lesioning data, conference participants concluded that studies comparing the outcomes of focal lesions versus DBS are ethical in part because of the high initial and ongoing costs of

DBS technology (e.g., for regular battery replacements), which make it unavailable to those with inadequate funds or insurance coverage, in both the developed and developing world. The need for indefinite access to highly specialized teams makes DBS impractical for some patient populations. DBS also carries risks and burdens, such as stimulation interruption due to battery depletion, not present in lesioning. As such, researchers should investigate treatments that might produce equivalent results without DBS's high costs and ongoing need for follow-up care. That said, and in contrast to lesioning approaches, DBS does have the clinical and ethical advantage of being potentially reversible (barring serious adverse events related to surgery). This is a relevant consideration for comparative studies of DBS and lesioning approaches both for targets that have and have not been prior targets of lesioning, and must be weighed along with the other factors mentioned above when considering such studies.

4. Given its history, neurosurgical intervention for disorders of MBT is a socially and culturally sensitive area of research and practice. Therefore, DBS for disorders of MBT should be studied in carefully designed trials, and should be performed only at expert centers that are participating in such trials and that adhere to the highest scientific, clinical and ethical standards.

   The impetus for the consensus conference was the perception that there is something unique about the use of DBS in patients with MBT partly because of the lingering influence of the troubled history of psychosurgery[23] and also because psychiatric patients are often considered a vulnerable population. Although there was both a scientific rationale and claims of benefit in early studies of psychosurgery, the rapid embrace and widespread adoption of so-called lobotomy surgery (20,000 cases in the US by 1950), without much evidence of efficacy or efforts to evaluate side effects, caused significant harm[23,24]. Subsequent peer-reviewed case series in the 1950s-70s reported response rates to psychosurgery of 50 to 80% for severe depression and 30 to 80% for severe OCD[21,25]. Consequently, particular caution was emphasized against an overly enthusiastic approach to recruiting severely incapacitated and vulnerable patients. Further, special safeguards for subject selection and the consent process are needed in the early investigational use of DBS for disorders of MBT.

5. DBS for disorders of MBT should only be performed by multidisciplinary teams working in close collaboration[26-28]. At minimum, the team should include:

   - Neurosurgeons and neurologists with extensive experience in DBS;
   - Psychiatrists with expertise in diagnosing and treating the psychiatric condition under investigation;
   - Both of the above groups should have experience in neurosurgical treatment for psychiatric disorders. If not, close consultation with experienced centers is strongly encouraged; and,
   - Neuropsychologists and case managers should participate in both pre-enrollment evaluation and post-study follow-up.

   Moreover, if DBS for disorders of MBT becomes a non-investigational procedure, hospital accreditation agencies should establish quality criteria and require any hospital performing DBS to meet criteria for team composition, as well as the standardized collection of outcomes and long-term follow-up data.

   Conference participants concurred that the complexity of the intervention and the disorders of MBT for which DBS would be used necessitates a team approach to the evaluation of potential recipients, the implantation procedure, programming and adjustment of concomitant medications and on-going monitoring. Potential subjects

should have a thorough preoperative evaluation and comprehensive post- and peri-operative team management, and an experienced surgical and clinical team should be required for all procedures, including those performed under humanitarian exemptions.

6. At present, patients should not undergo DBS for disorders of MBT without participating in an established, duly constituted, independently reviewed research protocol. DBS performed for compassionate or humanitarian use in single or small groups of patients should not be exempted from independent ethical review and oversight.

   DBS for disorders of MBT is off-label. Conference participants felt that the lack of studies demonstrating efficacy argues against offering the procedure outside of duly constituted research studies. However, in the United States, an FDA humanitarian device exemption application for DBS for OCD is pending. Approval of a humanitarian exemption would make wider scale use possible in centers that have institutional review board approval. In Germany, the Heilversuch (“Healing Trial”) exemption allows a practitioner to treat up to 10 patients without a hospital ethical review board's consent. We believe that all use outside a research protocol should undergo ethical review board oversight. How this is accomplished will be highly context-dependent, but one possibility is to limit the use of DBS for disorders of MBT to institutions with established ethical review bodies.

7. Inclusion criteria for trials of DBS for disorders of MBT will vary by disease and may change as data accumulate, but at present, inclusion should be limited to adults.

   While DBS is already appropriately used in the treatment of severe dystonia in children the prognosis is known and the disability is severe and permanent[29], conference participants were in general agreement that trials of DBS for disorders of MBT should be reserved for adult patients. The course of disorders of MBT can be particularly variable in young individuals, and the effects of DBS on the developing nervous system are unknown. The vast majority of people with Tourette syndrome have meaningful clinical improvement in late adolescence and early adulthood[30]. There are similar data demonstrating that OCD improves over the life of an affected individual[31]. Children are particularly vulnerable to their parents' perception of disease severity. Clinicians working with children and their parents need to be mindful that parents of children with early onset psychiatric disorders may not fully appreciate the long-term, even lifelong, consequences of DBS in a child. If DBS is found to be safe and effective for adults, then it might be appropriate to investigate its benefit for a younger population with severe, treatment-refractory symptoms. Exceptions should only be granted with formal oversight by an institutional review board or hospital ethics committee.

8. Because DBS for disorders of MBT is at the proof-of-principle stage, and its safety and efficacy have not been established, potential subjects in studies of DBS should be evaluated carefully and thoroughly to include:

   - A review of all available records;
   - Information from the patient's clinicians to establish a baseline assessment of disease severity;
   - Documentation of comorbidities;
   - Documentation in the patient's history of the failure of adequate (both for dosage and duration) therapeutic courses of multiple classes of treatment;

- A comprehensive evaluation that concludes that the patient's condition is severe, chronic, disabling and intractable; and,
- An assessment of the patient's social situation, its impact on illness severity and vice versa, and the potential for meaningful recovery.

Preoperatively, the DBS team should follow the patient for sufficient time—participants suggested at least 6 to 8 weeks—to establish a baseline and to thoroughly document that the patient meets the study inclusion criteria. The definition of treatment refractoriness will vary by disorder; specific recommendations have been published for the evaluation of patients with Tourette syndrome and OCD[14,26]. The goal of the evaluation phase is to ascertain that the patient meets diagnostic criteria without atypical features or significant comorbidity; that the patient is refractory to standard evidence-based treatments; and that the disorder is chronic, severe, and disabling to the point of justifying participation in a high-risk study. Participants noted that the scientific and patient-safety priorities are in harmony on this point, meeting the research aim of selecting patients with well-characterized symptoms and addressing the ethical goal of restricting high-risk experimental interventions to severely disabled patients who have exhausted their therapeutic options[32]. Consensus could not be reached on whether the review and evaluation should be conducted by the study team or an independent group of experts.

9. In addition to disease-specific symptom outcomes, outcomes in domains such as activities of daily living, cognition, quality of life, and global improvement (including family and patient perception) should be considered. At present, no single outcome measure can be identified as optimal for any disorder of MBT, although current clinical trials standards for each disorder are likely useful starting points (e.g., Hamilton Depression Rating Scale and the Yale-Brown Obsessive Compulsive Scale).

Consensus was not reached on which outcome measures should be used. Participants did agree that assessments of mood, behavior, and cognition should be included in all studies, in addition to scales measuring disorder-specific symptoms, to ensure that adverse neuropsychiatric events are prospectively identified and reported. Although there is no universally accepted scale for this purpose, meta-scales such as the Clinical Global Impressions and Global Assessment of Functioning are among the most commonly used across the various disorders and disciplines. Participants also agreed that measures of overall functioning (e.g., the ability to perform activities of daily living) should be included to fully capture the clinical outcomes of DBS for disorders of MBT. New assessment tools may be needed for this purpose. While none of the existing outcome measures is ideal, it is ethically incumbent upon clinicians and investigators studying DBS for psychiatric disorders to utilize well-validated and standardized outcome measures and to collect and share outcome data to facilitate later meta-analyses.

10. Within each expert center, researchers should consider using a standardized consent instrument and establish processes to assess potential subjects' capacity to consent. These methods should take into account the potential confounds of cognitive impairment and psychosis. Though the use of an independent review process to assess capacity may be appropriate in some studies, it is not necessary for all DBS studies involving disorders of MBT.

An independent review panel for patient selection and evaluation of patients' capacity to consent to research participation has been recommended for DBS in OCD[27]. A majority of conference participants felt that DBS research for disorders of MBT is equivalent to studies of other early phase therapies, and no patient safety protections

beyond those required for such studies is necessary, although there was some disagreement on this point. Reasons in favor of formal procedures to assess consent include the complexity of current studies of DBS and the perception that people with severe psychiatric illness are vulnerable to undue social influence.

11. There is no evidence that patients with disorders of MBT currently considered for DBS trials are unable to consent to early-phase, complex, high-risk DBS research simply by virtue of their diagnosis. Specifically, with regard to capacity to consent, there is evidence that, as a group, patients with treatment refractory depression are similar to other patients with life-threatening, severe, chronic disease[33-36]. Furthermore, there are no data to suggest that, in aggregate, patients with OCD or Tourette syndrome are different from patients with other chronic treatment refractory, debilitating conditions in capacity to consent. Nonetheless, given concerns about prior abuses of psychosurgery[23,24], an IRB-approved assessment of capacity should be carried out for each potential subject in early phase studies of DBS. In addition, it is recommended, though not required, that protocols specify the inclusion of "a close third" (often the patient's caregiver or partner) in the process of providing information and obtaining (witnessed) informed consent.

It has been hypothesized that disorders of MBT may impair the capacity to give informed consent; for example, it might be supposed that the apathy that characterizes severe depression interferes with evaluation of potential harms. However, data suggest that even though patients hospitalized for major depression have decreased decisional capacity, *as a group*, most scored above the cutoff point for determining incapacity[33-36]. A key point in several of these studies is that decision-making abilities are not correlated with depressive symptoms. No formal research has been done to evaluate the decision-making capacities of people with OCD or Tourette syndrome, but there is no evidence for characterizing them as more psychologically vulnerable or cognitively impaired compared to other chronically ill individuals. Treatment-resistant depression is a risk factor for suicide[37] and there have been reports of elevated rates of suicidal ideation, attempts, and completions in patients undergoing DBS regardless of indication[1]. Therefore, suicidality should be assessed in all individuals participating in DBS research and treatment, and the risk of suicide in those undergoing DBS assessed in long-term follow-up studies.

12. The consent process should include discussion of what is and is not known about long-term consequences of DBS. Potential adverse outcomes include potentially limiting participation in future research, inability to utilize certain other treatments (e.g., pacemakers) and an inability to undergo certain tests (e.g., some MRIs, currently). Consent documents should explicitly describe the conditions under which investigators would recommend discontinuation of stimulation and even removal of the device. Additionally, the consent process should state explicitly that, even with positive outcomes, DBS for disorders of MBT is unlikely, by itself, to improve all aspects of the individual's mood, function and interpersonal relationships: DBS is only one aspect of a comprehensive treatment program.

While acknowledging that this is a quickly changing field, participants generally concurred that the consent discussion should raise the issue of the opportunity costs of implantation, even though these may be generally true for all implanted devices. Currently, it is recommended that DBS patients not have an MRI on most scanner types, and this may be an important consideration for patients with other chronic diseases. Several participants raised the concern that some subjects will expect immediate and dramatic recovery, whereas results to date suggest that subjects often require extensive psychosocial rehabilitation. Because of the dramatic nature of the intervention and the risk of unrealistic expectations, special attention must be given

throughout the informed consent process to the identification – through conversation and direct questioning of potential subjects' understanding of a protocol and motivations for participation – and correction of false beliefs and therapeutic misconceptions.

13. Studies to determine the long-term safety of DBS are essential. Research protocols should include support for such studies for 5 to 10 years of follow-up. Preferably, follow-up data should be collected at 1, 2, 5, 10, and 15 years.

Participants noted that the longest follow-up for patients receiving DBS for OCD is 10 years; for depression, there are approximately 5 years of follow-up data on at least 10 patients. As more patients with psychiatric disorders undergo DBS, study protocols should mandate and support extended follow-up. Loss to follow-up among appropriately selected subjects in DBS studies is likely to be low since those with good outcomes will require periodic battery replacement and device maintenance. However, care must be taken to avoid a positive bias, if those with poor outcomes are lost to follow-up.

While research subjects have the right to withdraw from a study at any time, investigators have an obligation to encourage and support patients' participation in long-term follow-up studies. All subjects should be educated about the importance of continuing in long-term follow-up both for their own safety and for their potential contribution to research progress.

The principle of respect for persons requires informing research subjects of study results. Keeping subjects informed of the study's findings sends a message of transparency and partnership that can promote participation in long-term follow-up.

14. An independent registry of de-identified data on all individuals undergoing DBS for disorders of MBT should be established. In addition, regulatory agencies should require that device manufacturers collect long-term follow-up data on safety and efficacy. Physicians performing DBS for disorders of MBT have an obligation to collect prospective short- and long-term follow-up data, including both therapeutic and adverse effects. All of these data must be made publicly available.

As with other investigational or off-label interventions, there is likely a publication bias favoring reporting of positive outcomes in this field. Participants agreed that a DBS case registry will be essential for monitoring long-term safety and efficacy.

15. There should be no financial barriers or burdens to patients' withdrawing from a study and responsibility for long-term costs of device maintenance must be explicit. Manufacturers, third-party payers, researchers, research institutions, and funding organizations have an ethical obligation to determine and state who will be responsible for the costs incurred (e.g., for device removal if necessary, long-term maintenance of the device, and costs secondary to adverse events). Research subjects should not be responsible for costs associated with withdrawal and must be informed in the consent process about the availability of continued support for post-trial stimulator maintenance.

There are unique consequences of withdrawal from a trial of any implanted device; for example, the subject's right to withdraw is limited if she is personally responsible for related costs. Conference participants debated where the responsibility should lie. Some participants concluded that device manufacturers should bear the financial burden since they stand to make a profit, whereas others countered that research institutions profit from devices on which they hold patents or from facility use fees, and that researchers themselves may profit in career advancement after publishing a major study. Some participants stated that Medicare and third-party insurers also had

a stake in supporting research and caring for research subjects. One suggestion was that all stakeholders (except subjects) contribute to a general fund or insurance policy to cover subjects' costs associated with implantable device trials.

When study protocols appropriately include a long follow-up phase of 5, 10, or more years, it is debatable whether the patient continues to be a research subject with the same rights to device withdrawal and device maintenance as a subject in the active phase of a study. The costs of meeting the discussed ethical obligations will likely exceed the willingness or capability of not-for-profit or for-profit entities. However, disabling, treatment-refractory illness is a financial burden for society as well as the individual and family[38].

16. Presently, no recommendation can be made about patient control of stimulation, but this topic should be studied further. Information on this topic should be included in the consent process for each study.

Given the ethical and practical constraints on performing sham surgeries, particularly in awake patients, randomized controlled trials of DBS are likely to utilize a crossover design in which the comparison condition will be individuals who have the device implanted but not yet activated. Ethical difficulties arise when patients break the blind to learn that their device is turned off, and then withdraw from the trial in order to have it turned on. The implantation of a device that can be turned off but not removed without risk is clearly different from a drug that can be stopped without harm. The subject who has been surgically implanted has undergone the surgical risk and the burden of the implantation, and one can debate what the ethical rights and obligations of patient and investigator should be.

With DBS for some movement disorders (e.g., essential tremor), some people turn the device down at night in order to preserve battery life. In addition, the device must be turned off during certain diagnostic tests (e.g., EKG, EMG). However, there is as yet no data demonstrating whether self-control of the device would be beneficial for patients with other disorders.

Conclusion

Conference participants recognize that the implementation of these guidelines will require a commitment from clinicians, investigators, institutions, industry, funders and government regulatory agencies. Several recommendations involve a substantial burden of long-term monitoring and financial support to protect the safety and rights of research subjects. However, following these guidelines has the potential to benefit research subjects, their social supports, future patients, clinical investigators, and device manufacturers, by ensuring that this promising technology is studied in carefully defined settings where it is more likely to offer benefit and less likely to harm.

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