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.

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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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{34} Recommendations have been developed by various consortiums in regards to protecting and selecting patients.\textsuperscript{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 – 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\textsuperscript{39} that would preclude them from enrollment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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”.\textsuperscript{43} 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.\textsuperscript{43} Informed consent can be challenging in psychiatric disorders,\textsuperscript{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.\textsuperscript{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.\textsuperscript{44,48} Furthermore, for those with reduced capacity, the decision-making abilities can be compensated by more intensive educational interventions\textsuperscript{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.\textsuperscript{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”.\textsuperscript{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,\textsuperscript{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.\textsuperscript{53–55} Overall, adverse effects secondary to DBS tend to be transient.\textsuperscript{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.\textsuperscript{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.\textsuperscript{58} Long-term complications are also possible, including infection, erosion, loss of effect, intermittent stimulation,
tolerance, pain, or discomfort. A patient’s support system must also be abreast of their responsibilities and time commitment, so they can be optimized in the process, and be referred to resources as needed. Patient autonomy, informed consent, beneficence, and non-malefeasance must all be balanced; with potential patients adequately informed that enrollment in research trials may or may not produce any perceptible medical benefit.

4. Design of clinical trials

The reversible nature of DBS permits randomized, double-blinded trials, with both between- and within-group comparisons in the “on” and “off” device states. Enrolling patients in a trial where they undergo implantation of electrodes presents an ethical dilemma, especially in terms of informed consent and beneficence, as certain patients may serve as controls with their electrodes inactive. While this group may be medically managed during a trial period, they will have undergone the risks associated with invasive brain surgery without the potentially immediate and direct effects of DBS. Additionally, bias may be introduced into the trial because during implantation test stimulations are performed to assess functionality and adverse effects. It is possible that a number of patients may know how they have been randomized because they have sensations of the electrode turned “on” in the operating room or pre-randomization testing to determine optimal stimulation parameters. Patients may feel acutely better or at least sense a change in the operating room during test stimulations and implantation and therefore later know the state of their stimulator regardless of blinding. How this might complicate assessing trial results is unknown, but remains a limitation. A pure way to correct this would be to implant and not test the electrode, but given the ethical and practical constraints of sham surgery, a crossover design or an initial observational trial using independent assessors may have to suffice.

There is a difference in stopping a drug without harm as compared to turning off a device that requires removal. Clinical trials to assess the safety and efficacy of DBS raise ethical questions regarding the acceptable level of risk for minimal or no benefit, the use of placebo controls, the reversibility of surgery, the duty to provide care once a study ends to those patients who report benefit and determining proper endpoints for studies. A key feature of DBS is that its risks are overall better than most surgical procedures. In general, risks appear to be low and most adverse effects are secondary to active stimulation and not the surgical procedure. Side effects are usually reversible by adjusting stimulation parameters. To our knowledge, most complications are seen in older patients, including those with cognitive decline, whereas patients with dystonia and ET who are younger, with normal sized brains and no dementia encounter far fewer problems.

5. Intrinsic identity, personhood, brain enhancement, and social expectations

The reversible nature of DBS provides patients with the possibility of adjustment, titration, and even turning off the stimulation. A somewhat unique ethical question that arises is during research trials how much control should patients have over their device within a safe threshold window secondary to the principles of beneficence and patient autonomy? That is, should patients be in control of their own brain when a medical device is implanted or should physicians remain the sole source of deciding when to have the pulse generator “on” and “off”? For example, devices such as Medtronic’s Kinetra (Medtronic, Minneapolis, MN, USA) internal pulse generator provide patients the option of self-adjusting, though the frequency at which patients use this option and its overall value is under investigation. More recently, newer devices, such as Medtronic’s Activa PC and SC batteries can deliver constant current stimulation. Given the wealth of data suggesting a lack of impedance stability over time, constant current mode may have significant advantages over constant voltage. Rechargeable batteries have also recently become available, increasing the average lifetime of the battery from 3–5 years to 9 years, and thus attenuating the rate of unpredictable battery depletions.

Besides this ethical dilemma, philosophical notions of self and personal identity must be addressed. Does identity revolve around someone’s demeanor, attitude, and feelings? That is, in the case of depression, is a person, who through genetic and environmental factors, no longer the same person if his or her neurochemistry is modulated electronically, or otherwise? These questions of self have been addressed in thought experiments such as the “Brain in a Vat” popularized by Hilary Putnam, which later formed the premise for the Matrix trilogy. These presentations locate the self as what one is neurochemically experiencing, regardless of how, or for that matter where, those neurochemicals are generated.

In modifying the brain how much of one’s established personality can be changed before others fail to recognize the person as the person they knew prior to treatment? Are patients on anti-depressant medications no longer the same person, as discussed in the book Listening to Prozac? These individuals are modulating their neural networks with drugs under the guidance of their prescribing physician. Who is to say whether improvements in symptoms constitute a “cure”, a transformation, or an obliteration of the self? That is, how much change in personality is consistent with maintenance of personal identity remains a novel challenge, and one that is likely to be increasingly troubling.

In a similar vein, should devices ever be put into the pleasure centers of the brain or memory circuits to enhance “normal” people? It has been demonstrated that hypothalamic stimulation modulates limbic activity and improves certain memory functions in human patients. A negative impact on cognition, specifically verbal and executive memory, has been reported in scattered studies of PD patients treated with subthalamic nucleus (STN) DBS. Should individuals with DBS for affective disorders be given self-control of the device so that regardless of symptoms they can “enhance” themselves? Should we worry if someone increases the power of the impulse generator before a speech or is having a bad day and turns up the generator to feel better? Should people have direct control to their pleasure centers, thereby circumventing the standard course of pleasure production? Society clearly accepts modulation with caffeine and anti-depressants, as well as alcohol, and now in some states marijuana. So would enhancement through DBS always be inappropriate? This is a slippery slope that requires caution in this respect as demonstrated by street drugs. Nevertheless, depression can be extremely incapacitating.

Major depressive disorder is known to be one of the most disabling and common psychiatric diagnoses, with a current prevalence in the Americas of 9–21%. Approximately 15% of these depressed patients will later present with treatment-refractory depression, with continued therapy failure potentially becoming life threatening as suicidal thoughts and suicidal planning emerge. DBS in this select patient group may not only improve the quality of life for many individuals, but could also save the lives of those who would otherwise kill themselves. Several studies have documented an overall reduction in depression post-STN DBS at 1–3 years, though a follow-up study at 5 years reported no overall change. Studies of globus pallidus internus DBS, with the caveat of having small sample sizes, demonstrated no overall change in the level of depression in PD patients. Long-term follow-up of DBS of the subcallosal gyrus revealed durability of benefit in depression with an approximately 60% responder rate.
ever, in some trials, patients committed suicide prior to the end of the study phase, inciting significant concern for the role of the DBS in the suicides.\textsuperscript{46,47} However, the rate of suicide was no higher than the rate of suicide amongst treatment-resistant patients with depression. These studies inherently are of limited value as many lack a non-DBS control group and “mean” mood is hard to quantify. Nevertheless, even though the results are preliminary and weak, for patients in life-threatening situations, the benefits of potential alleviation could outweigh the risks.

The social implications of depression can be profound, with immense potential impacts on the spouse, profession, and other societal relationships. On the other hand, as we have seen with medication for depression, making a person feel better may increase the risk for treatment-emergent suicidal feelings and potentially an increased rate of suicide attempts or completed suicide. These unknowns – risks – must be characterized as we document cognitive and behavioral changes related to the social impacts following DBS. With an emphasis on preserving and respecting autonomy, the core ethical question may be - does DBS alter personality in a positive or negative way from the patient's perspective?

6. Resource allocation

DBS costs approximately $USD80,000 per patient.\textsuperscript{88} Absenteeism due to depression alone is responsible for billions of dollars lost per year in the USA. Treating depression reduces the number of days that patients are unable to work and this may at least in part make up for the costs of treatment. While the cost of DBS is high, the social toll exacted by depression and OCD may well make this the treatment of choice for severe, refractory patients should it prove efficacious.

Societal pressures will likely help guide how and for whom DBS is applied. If a depressed person is suicidal and deemed incapacitated, can a court actually order DBS against the patient’s will for the benefit of the patient? What about modulating reward circuitry to “tone down” sexual criminals, parolees or murderers? Can prisoners be mandated to have neuromodulation as part of their rehabilitation? In all these scenarios, the informed consent process should remain intact. However, vulnerable populations such as prisoners or repeat offenders may see their rights abrogated in the hope of achieving a “quick fix” to their behavior.

The media often shapes public attitudes about the use and funding of new medical technologies. However, usually only the miracle stories are reported,\textsuperscript{89} and in this regard the media will likely shape how DBS is looked upon.\textsuperscript{22} For example, electroconvulsive therapy has been painted in a negative light so many times that even today, the majority of the public view it as harmful,\textsuperscript{90} even though it is not scientifically controversial and has been shown repeatedly to be one of our most efficacious treatments for severe depression.\textsuperscript{91} Investigators working with DBS have an obligation to work with the media to try and ensure accurate information is provided to the public and policy makers.

7. Conclusions

DBS may be an effective surgical treatment for psychiatric disorders, such as OCD and TRD. There are many ethical questions that must be fully addressed in designing clinical research trials. These include the selection of research patients, ensuring informed consent, clinical trial design, the use of placebo controls, concerns about altering personal identity, the potential use of DBS for brain enhancement, and cost and resource allocation. DBS provides a unique opportunity to not only ameliorate disease but also to study mood, cognition, and behavioral effects in the brain. It is crucial to maintain sound ethical boundaries in this new era so as to permit the proper testing of the potential therapeutic role which DBS may play in ameliorating these devastating and frequently treatment-refractory psychiatric disorders.

Conflict of interest/disclosure

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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