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A Future for Neuromodulation in Psychiatric Disease

The Psychiatric Neurosurgery Committee and Board of Directors of the American Society for Stereotactic and Functional Neurosurgery (ASSFN) would like to express their enthusiastic and unwavering commitment to research exploring the neuromodulatory treatment of psychiatric disease. The field has encountered recent challenges, with the discontinuation of two pivotal trials evaluating the efficacy of deep brain stimulation (DBS) for the treatment of depression. An unintended consequence of the discontinuation of these two trials is the interpretation by the public, industry, regulatory bodies, and health care professionals, that trial discontinuation represents a failure of the therapy, rather than just an unsuccessful trial. These perceptions may in turn result in a nihilistic approach to future therapeutic trials. Consequently, patients may despair that there is little hope for new successful treatments. In contrast, we continue to believe that there is great promise for the therapeutic application of neuromodulation to diseases of mood, behavior, and cognition. We wish to reassure the many sufferers of psychiatric disease that we are committed to untangling these complex disorders and remain steadfast in our conviction that neuromodulation will ultimately be an important therapeutic modality.

There is a natural inclination to interpret the closure of a trial as failure of a therapy. However, we must distinguish between the failure of a therapeutic strategy and an unsuccessful implementation of that particular strategy. The success of a trial is influenced by many variables, only some of which are inseparably tied to the fundamental treatment strategy. As such, the recent trial closures should prompt a committed examination of trial design rather than being viewed as a categorical indictment of the proposed therapy. To assume that the treatment itself has failed does not account for the many factors that influence success, within the very tight constraints of blinded, randomized studies. These include patient selection, disease variability, surgical technique, resolution of the

effects of surgery itself, selection of endpoints, duration of follow-up and placebo effects, to name just a few. These factors, alone or in combination, can result in dilution of therapeutic effect in these relatively small cohorts.

Fundamentally, we share the belief that diseases of mood and behavior are produced by aberrant function within circuits of the frontal and limbic cortices and the basal ganglia. Although our understanding of this pathophysiology remains limited, the evidence supporting this conceptualization continues to accumulate with each new trial. Pivotal studies with binary outcomes, that are designed to yield either a 'yes' or 'no' conclusion may fail, while unknown complexities confound the consistency of a potentially safe and effective therapy. We have every confidence, however, that future trials with more targeted outcomes and the potential for adaptive trial design will continue to unravel the mysteries of psychiatric and neurological disease, and that emerging technologies will provide us with ever more refined tools to exploit this growing understanding. We anticipate that the implementation of such modifications to trial design in future studies will ultimately result in successful therapies.

The ASSFN Board of Directors has begun a dialogue with the leadership of the neuromodulation industry. There is a shared belief in the therapeutic potential of neuromodulatory approaches to psychiatric disease and a universal acknowledgement of the need for more refined, innovative, and effective solutions. Ultimately, progress will require a partnership between academia and industry to produce viable solutions for the treatment of psychiatric disease. We are fortunate to have thoughtful and committed partners in these future endeavors. Through such collaborations, we are eager to continue working to design successful treatments.

Finally, the ASSFN recognizes the perseverance of patients affected by depression, OCD and other psychiatric disease. We are acutely aware of the unremitting disease burden and are completely committed to finding therapies that address this unmet need. We appreciate the patience of the public, industry, regulatory bodies, our colleagues, and above all, the patients we are attempting to serve and ask for your support and partnership in advocating for and exploring this growing area of scientific and clinical discovery.

Sincerely,

The Psychiatric Neurosurgery Committee and
Board of Directors of the ASSFN