Deep brain stimulation for obesity: rationale and approach to trial design

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Obesity is one of the most serious public health concerns in the US. While bariatric surgery has been shown to be successful for treatment of morbid obesity for those who have undergone unsuccessful behavioral modification, its associated risks and rates of relapse are not insignificant. There exists a neurological basis for the binge-like feeding behavior observed in morbid obesity that is believed to be due to dysregulation of the reward circuitry. The authors present a review of the evidence of the neuroanatomical basis for obesity, the potential neural targets for deep brain stimulation (DBS), as well as a rationale for DBS and future trial design. Identification of an appropriate patient population that would most likely benefit from this type of therapy is essential. There are also significant cost and ethical considerations for such a neuromodulatory intervention designed to alter maladaptive behavior. Finally, the authors present a consolidated set of inclusion criteria and study end points that should serve as the basis for any trial of DBS for obesity.

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KEY WORDS deep brain stimulation; obesity; lateral hypothalamus; nucleus accumbens; Prader-Willi syndrome

OBESITY is defined as a body mass index (BMI) greater than 30 kg/m². Recent estimates suggest that the prevalence of obesity in the US is greater than 35%,¹⁹ with more than 500 million obese individuals worldwide.⁸⁶ Obesity has been linked to an increased risk of hypertension, hyperlipidemia, Type 2 diabetes, stroke, coronary artery disease, and a variety of cancers.^{9,31} Furthermore, health care expenditures in obese individuals are as much as 45% higher than those in lean individuals, and economic-based models have estimated that health care costs related to obesity total \$75 billion per year in the US alone.^{34,94} Based on these data, obesity is one of the most pressing public health concerns.

The standard of care, first-line treatment for obesity is lifestyle modification.⁴⁰ While dietary treatment can be effective in the immediate short term, the vast majority of patients fail to achieve sustained, long-term weight

loss.² The success rate of dietary treatment is increased somewhat when combined with adjuvant group therapy, behavior modification, and/or active follow-up. However, the majority of patients ultimately relapse after an initial period of weight loss.² Bariatric surgery is indicated in patients with BMIs greater than 40 kg/m² (or > 35 kg/m² in the presence of obesity-related comorbidities) who have undergone unsuccessful nonsurgical treatment.¹⁸ These procedures have been found to be superior to behavioral modification alone,¹³ and thus the number of bariatric procedures performed in the US has increased 10-fold over the past two decades.⁵⁰ Bariatric surgery is one of the only effective treatments for long-term weight loss in morbid obesity.¹⁴ As a result, there has been an increasing demand for these surgical procedures. Failure of bariatric surgery is most often defined as less than 50% of excess weight loss at 18 months after the operation, with or without a

ABBREVIATIONS BMI = body mass index; DBS = deep brain stimulation; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; LH = lateral hypothalamus; NAc = nucleus accumbens; OCD = obsessive-compulsive disorder; PD = Parkinson's disease; PWS = Prader-Willi syndrome; QALY = quality-adjusted life year; VMH = ventromedial hypothalamus; YFAS = Yale Food Addiction Scale.

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BMI greater than 35 m/kg².⁵¹ Nonetheless, the rates of both short-term and long-term morbidity of bariatric surgery are not insignificant.^{21,74} While reported failure rates are highly variable in the literature and further depend on patient selection, degree of obesity, and surgical technique,^{1,12} relapse of metabolic syndrome and weight regain occur in as many as 35% of surgically treated patients at long-term follow-up.²⁸

Radiological Evidence

Both the hypothalamus and the nucleus accumbens (NAc), two brain regions with known interconnections, have been implicated in imaging studies of obese humans.³² Sweet tastes such as glucose, sucrose, and other palatable tastes, as well as images of calorically dense food, induce abnormal responses in the NAc and hypothalamus in obese patients compared with lean controls.^{30,52,78} Moreover, the serotonin noradrenaline reuptake inhibitor sibutramine results in attenuated hypothalamic response to high-calorie food images, and this attenuation correlates with the drug's impact on weight and eating behavior in obese patients. Additionally, satiety after a meal attenuated the NAc response to high-calorie food images, which also correlated with eating behavior.²⁰ Thus, change in the activity of these regions is linked to change in behavior, making them a promising target for intervention.

Murdaugh and colleagues found that a greater NAc response to high-calorie food images predicted poorer treatment response in obese patients undergoing behavioral weight-loss treatment.⁶⁰ One study examining brain function in patients receiving bariatric surgery found that abnormalities in hypothalamic response to food images present in obese patients were not found more than 1 year after Roux-en-Y surgery.²² Furthermore, reduced NAc response to high-calorie food images was associated with reduced palatability and appeal of high-calorie foods and healthier eating behaviors among patients after Roux-en-Y surgery.⁷² Taken together, these findings further suggest these regions as promising targets for deep brain stimulation (DBS) to treat obesity, as their dysfunction appears directly associated with food stimuli and response to treatment.

Deep Brain Stimulation Targets for Obesity

Several potential DBS targets for obesity have already been identified through anatomical investigation of the appetite and reward circuitry of the brain, and studied in animal and human neuroimaging studies. Within the hypothalamus, the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH) have long been recognized as the feeding and satiety centers of the brain, respectively. Functional MRI studies have demonstrated the complementary actions of these regions in perpetuating obesity in humans.^{24,80} Additionally, studies of the behavioral and psychiatric pathophysiology of morbid obesity have also identified altered reward circuitry in the brain that may play a role in food craving, which is commonly observed in these patients.^{41,44} Feelings of craving, reward anticipation, and reward-driven consumption all involve neural circuitry between the prefrontal cortex, which houses the inhibitory control regions, and the striatum, within which

the NAc has traditionally played a prominent role in promoting reward-driven behavior.^{77,85} (Fig. 1)

In animal models, lesioning studies of the LH have revealed weight loss, and bilateral DBS in rats produced a significant weight differential compared with nonstimulated controls.⁶⁸ A recent pilot study of DBS of the LH in 3 morbidly obese patients who had previously failed gastric bypass surgery was completed. While the study was designed to assess safety and not efficacy of DBS for obesity, stimulation parameters of the LH were optimized to induce a sustained increase in resting metabolism with stimulation, after which weight loss was observed, and no detrimental psychiatric symptoms were detected.⁹⁰ In a similar fashion, lesions to the VMH have led to weight gain, increased adipose tissue, and hyperinsulinemia in animal models, with similar effects observed with high-frequency DBS in both murine and primate models.^{5,46} Low-frequency stimulation of this focus appeared to inhibit feeding behavior and increase weight loss in a wide variety of animal models, including in a recent study in primates in which Torres and colleagues proposed an intraventricular “floating” electrode inserted in the third ventricle contiguous to the VMH. Stimulation delivered to the VMH has been shown to evoke emotional panic attack-like behavior with autonomic disturbances in both animals and humans, which may preclude its suitability as a human DBS target for obesity.^{71,92} Nevertheless, VMH target refinement is already underway in some centers. Finally, lesioning studies involving the NAc have led to promising results in animal studies with elimination of food-hoarding behavior and significant weight loss.⁴³ Furthermore, proof-of-concept DBS studies of the NAc specifically aimed at examining its effects on feeding behavior found a significant decrease in binge-eating behavior, as well as decreased caloric intake and sustained weight loss in obese mice. These authors also found that these stimulatory effects involved D2 receptors.³² Moreover, the NAc is a well-validated DBS target with a good safety profile that has been exploited for treatment of such processes such as treatment-refractory depression, obsessive-compulsive disorder (OCD), and alcoholism.^{27,58,70} Given the link between obesity and the mesolimbic reward circuitry, further studies targeting the NAc with DBS, specifically for treatment-refractory obesity, should be considered promising.

Cost and Ethical Considerations of DBS

Cost Considerations

In our current health care delivery paradigm, costs must be included in the consideration of any novel treatment modality. In evaluating the fiscal efficacy of DBS, it is reasonable to examine data comparing DBS to medical management of Parkinson's disease (PD). Several studies have demonstrated the economic superiority of DBS over medical management in PD.

In terms of absolute costs, most recent cost estimates based on the Department of Veterans Affairs and Medicare databases are approximately \$17,000–65,000 for initial DBS surgery, with up to an additional \$17,000 in annual costs for the first 3 years. However, these data were extracted for patients with PD and encompass condition-

FIG. 1. Schematic diagram depicting the DBS targets for obesity and their role in the homeostatic pathway of energy balance in normal and PWS physiology. The cortical inhibitory control regions are located in the prefrontal cortex (PFC), and the subcortical reward circuitry in the nucleus accumbens (NAc), and lateral hypothalamus (LH). The LH is responsible for providing anabolic feedback onto the autonomic nervous system effectors. The NAc is the center of the reward pathway in the brain, integrating inputs from various higher cortical brain areas and the limbic system to reinforce certain beneficial behaviors, such as feeding. Integration of the reward pathways with feeding behavior begins with dopamine release from the ventral tegmental area (VTA) neurons that project onto the NAc. Within the NAc, there are GABAergic neurons that project to the LH, which then contains neurons that drive food intake. These nuclei also respond to various hormonal peptides such as leptin, providing one of the many links between food intake and energy metabolism in the brain. In Prader-Willi syndrome (PWS), the normal cortical inhibitory control and subcortical reward circuitry are disrupted in response to food stimuli with hypoactivation of the PFC and hyperactivation of the NAc and LH compared with healthy individuals. GABA = γ -aminobutyric acid. Modified with permission from Ho et al: *Cureus* 7:e259, 2015.³⁶

specific costs as well.^{75,79} Tomaszewski and Holloway reported that DBS in PD becomes cost effective if quality of life is improved by 18% compared with best medical management.⁸² Meissner et al. retrospectively studied treatment costs in DBS in PD versus medical management.⁵⁵ They reported an increase in costs by 32% in the first year but a decrease by 54% in the second year. They further reported a decrease in overall medication expenses and improved efficacy in patients undergoing DBS.

In contrast, in a head-to-head study of more than 3600 bariatric surgery patients and comorbidity-matched, bariatric-surgery eligible controls, initial costs associated with laparoscopic bariatric surgery were estimated at \$30,000, but postprocedure costs savings began to accrue as soon as 3 months after the operation. The initial investment costs for the procedure were returned within 2 years, and were

mainly associated with a decrease in health care utilization from obesity-related comorbidities. In addition, savings rates in the bariatric surgery cohort compared with controls increased to more than \$900 per month 1 year after surgery. This analysis did not include additional quality of life and length of life benefits, nor did it include cost benefits associated with decreased disability and unemployment.¹⁵ A separate study conducting an incremental cost-effectiveness analysis for bariatric surgery found that laparoscopic bariatric surgery was highly effective, with an associated cost of slightly more than \$6000 for each quality-adjusted life year (QALY) gained. This favorable cost-effectiveness result was maintained even in complete weight regain scenarios, with an incremental increase to \$24,000 for each QALY gained.⁸⁹ In considering DBS as an adjunct treatment following bariatric surgery failure,

there are clear cost gains to be achieved as long as similar and more enduring weight-loss results are achieved. However, given the higher surgical costs associated with DBS, there will likely be a longer interval to return on investment, as well as higher costs for each QALY gained compared with bariatric surgery.

With only a few reports of DBS in obesity there are no similar studies of actual cost effectiveness. Pisapia et al. conducted a decision analysis comparing the two major surgical options for obesity: laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding.⁶⁵ Laparoscopic banding was found to not be effective at achieving successful weight loss (defined as at least 45% of excess weight), and the complication rates for gastric bypass surgery (33%) far exceeded those of DBS (19%). These reports characterize DBS in obesity as a promising therapeutic avenue from an economic standpoint. With lower complication rates compared with bariatric surgery, targeted neuromodulation could decrease long-term costs in the morbidly obese patient population, especially in patients who have already failed bariatric surgery.

Ethical Considerations

As indications for neuromodulation continue to expand, there will be an ongoing debate on the ethics of intervention. The neural circuitry of obesity overlaps with that of addiction, and this may raise concerns of patient autonomy in the context of behavioral alteration.¹⁰ Specifically, targeting the NAc may lead to alterations in reward pathways or withdrawal. A patient's ability to experience normal pleasure may also be diminished or perturbed. The ethical argument is similar to the one for OCD in which benefit-harm ethical arguments favor DBS in patients with high-level decisional capacity.²⁶ Moreover, autonomy may be fundamentally inadequate in individuals suffering from disorders of the reward circuitry, requiring experience-based paternalism on the part of doctors.¹¹

An alternative perspective for patient autonomy suggests that neuromodulation may actually restore patient capacity to make choices. For example, Uusitalo argues that there is a distinction between difficulty and freedom in the ability of a patient to make a choice. Using the example of cravings in addiction, she eloquently highlights the possibility that DBS may reduce the difficulty in controlling cravings but, importantly, will not change a patient's freedom to continue addictive behaviors.⁸³ Müller et al. has gone further to characterize DBS as actually granting "full autonomy" to the patient.⁵⁹

The ethical underpinnings of DBS treatment for obesity will be further challenged in the clinical-trial phase. Several key factors must be clarified prior to enrollment, including trial design, informed consent, and a greater discussion on the concept that DBS treatment would be a threat to patient identity.⁶⁴ As such, we advocate for a multidisciplinary team of surgeons, endocrinologists, obesity specialists, neuropsychiatrists, and ethicists to provide longitudinal guidance for delivering ethical and high-level care. We believe that in an appropriately selected population of patients who are refractory to medical and surgical management of morbid obesity, there is a role for DBS. There must be stringent inclusion criteria, informed consent, and clinical equipoise in conducting clinical trials.²⁹

Target Patient Population

A safety and feasibility trial of DBS for obesity in humans should involve those patients who have undergone unsuccessful bariatric surgery (specifically gastric bypass) due to persistent binge-eating behavior. Predictors of bariatric surgical failure have been studied extensively and include age, sex, preoperative BMI, substance abuse, compliance with follow-up appointments, eating habits, physical activity, and psychiatric status.⁸⁹ With respect to the latter, there is a growing body of evidence that patients with mood or anxiety disorders have higher failure rates after bariatric surgery.¹⁶ Furthermore, there is a high prevalence of "loss of control" or binge eating in those individuals who regain weight. Interestingly, bariatric surgery has been repeatedly shown to improve binge-eating postoperatively.^{53,87} However, at 2 years after surgery, Sallet et al. noted that the association between presurgery binge eating status and higher postsurgery weight regain are most clear.⁶⁶ The question remains whether ongoing maladaptive eating behaviors such as binge eating are critical factors in patients who fail bariatric surgery.²³ This would be the treatment-resistant population in which we could target DBS as a multimodality treatment for weight loss.

Demonstration of treatment resistance is essential for all potential DBS trial candidates.^{25,93} However, for obesity, identification of a particular etiology of treatment failure is also crucial, given that DBS treatment of obesity would occur via modulation of specific neural pathways (such as the reward circuitry). The Yale Food Addiction Scale (YFAS) is the most widely used and accepted tool to measure food addiction (Table 1).²³ It is based on the substance use disorder criteria in the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (DSM-V), and is similar to other compulsive activity scales.³⁸ There is increasing evidence in the literature to suggest that overeating may be a behavioral addiction similar to substance abuse that shares similar behavioral and neurobiological factors.^{84,95} Furthermore, there is evidence that scores on the YFAS are associated with brain response to anticipation of taste reward, although its relation to hypothalamic and NAc function has not yet been examined.²⁴ In addition to weight regain, postbariatric surgery patients are at increased risk for developing alcohol and substance abuse disorders^{45,68} that likely represent an "addiction transfer."⁹¹ The YFAS has been validated as predictive of continued emotional and binge-eating behavior following bariatric surgery.¹³ Furthermore, as noted above, the presence of binge-eating behavior after bariatric surgery is clearly associated with less weight loss and more weight regain.⁵³ Therefore, postbariatric surgery evaluation of food addiction behavior via the YFAS may aid in identifying a subpopulation of patients who had unsuccessful bariatric surgery that would most benefit from DBS of the NAc, given the addiction and substance-abuse nature of their disorder.

External eating (sensitivity to external food cues) is associated with higher food addiction scores and decreases in weight loss after bariatric surgery⁶³ and may be another measure to target in DBS trials for obesity. Passamonti and colleagues found that external eating scores modulated the connectivity between the ventral striatum and amygdala while viewing appetizing food images, suggesting an

TABLE 1. Components and scoring of the YFAS*

Substance-Dependence Symptom from DSM-IV†	No. of Questions‡	Normative %
Substance taken in larger amount and for longer period than intended	3	21.7
Persistent desire or repeated unsuccessful attempt to quit	4	71.3
Much time/activity to obtain, use, recover	3	24
Important social, occupational, or recreational activities given up or reduced	4	10.3
Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)	1	28.3
Tolerance (marked increase in amount; marked decrease in effect)	2	13.5
Characteristic withdrawal symptoms; substance taken to relieve withdrawal	3	16.3
Use causes clinically significant impairment	2	14

* Adapted from Gearhardt AN, Corbin WR, Brownell KD. Yale Food Addiction Scale (YFAS). Measurement Instrument Database for the Social Sciences, 2012. Retrieved from www.midss.ie. Copyright: CC BY-NC 3.0 (<http://creativecommons.org/licenses/by-nc/3.0/>).

† Number of questions within the YFAS addressing each symptom of substance dependence as defined by the DSM-IV, and the percentage of normal patients with each symptom (normative %).

‡ The YFAS scoring algorithm with a median symptom count was as follows: if scoring for a specific criterion is ≥ 1 , then the criterion for that symptom is met; substance dependence is considered when ≥ 3 symptom criteria are met. The normative percentage of normal patients surveyed with the scale that met YFAS criteria for substance dependence was 11.6%.

association between these brain processes and sensitivity to food cues, which could be improved through DBS.⁶²

Inclusion Criteria

Determination of appropriate inclusion criteria for a DBS obesity trial would be similar to previous studies published to date for other DBS trials for psychiatric indications.^{3,17,57} In most other disease trials for DBS, surgery was offered to patients with severe symptoms in whom medical therapy had failed, and who did not have any other major contraindications to DBS.⁴⁷ Trial design would largely depend on the proposed DBS target, but the need for a traditional Phase I clinical trial may be obviated by the fact that a reasonable safety profile has been largely established by previous pilot trials/studies of both LH⁹⁰ and NAc^{3,17} targets. Thus, proof-of-concept and efficacy studies would be the next logical step. Patients with general contraindications to DBS should be excluded (Table 2). DBS could be offered to adult patients with morbid obesity (BMI > 40 kg/m², or 35 kg/m² with comorbidities) in whom medical therapy and bariatric surgery have failed, with greater consideration given to patients with obesity-related comorbidities such as Type 2 diabetes mel-

litus, cardiovascular disease, obstructive sleep apnea, and others.⁵⁴

Given the close relationship between obesity and psychiatric disorders such as addiction, anxiety, and depression, as well as socioeconomic factors,⁶ patients would have to undergo extensive multidisciplinary evaluation prior to surgery including psychological and socioeconomic evaluation to ensure that appropriate perioperative psychological support is provided so that weight loss gains are sustained.^{42,61} Proposed evaluative end points of a study could include a wide range of biometric markers of obesity such as caloric consumption, resting metabolic rate, and immediate and sustained weight loss, but should also include evaluation of improvements in obesity-related comorbidities and psychological metrics, as well as improvements in overall quality of life (Table 3).

Prader-Willi Syndrome

Finally, given the severity of hyperphagia, the linked neural reward circuitry dysfunction, and the poor outcomes noted with bariatric surgery, patients with Prader-Willi syndrome (PWS) may represent an additional population of potential trial candidates that may most benefit from

TABLE 2. Contraindications for DBS

Contraindication
Recent myocardial infarction
Cardiac arrhythmia
Cardiac malformation
Epilepsy
Stroke
Degenerative disorder of the nervous system
Arterial hypertension or hypotension, not controlled by drugs
Autonomic nervous system disorder
Endocrinological illnesses
Major disturbances in electrolyte imbalance (e.g., due to renal insufficiency or hyperaldosteronism)

TABLE 3. DBS for obesity: proposed inclusion criteria and study end points

DBS Study for Obesity	
Inclusion criteria	
Failure of bariatric surgery w/ <50% of excess weight loss, w/ or w/o BMI >35 m/kg ² , at 18 months or more after the operation ⁵²	
Diagnosis of food dependence via YFAS criteria ²³ (Table 1)	
Normal neurological examination	
Normal head CT scan and cerebral MRI	
Patient not pregnant	
Psychiatric evaluation	
Socioeconomic evaluation	
Ethics Committee/Institutional Review Board approval	
Patient informed and gives written consent	
End points	
Immediate and sustained weight loss (BMI)	
Caloric consumption	
Resting metabolic rate	
Improvement in YFAS score	
Amelioration of obesity-related comorbidities	
Improvement in related psychiatric conditions (depression, anxiety, etc.)	
Quality of life	

a DBS intervention tailored around neuromodulation of these very same reward circuits.³⁶ Prader-Willi syndrome is caused by a genetic defect resulting in absent expression of several imprinted genes in the 15q11-q13 region from the paternal chromosome 15.⁴ The syndrome is characterized by extreme hyperphagia, obesity, and intellectual disability. Patients with PWS have insatiable appetites and are often morbidly obese.⁷ Nearly 1 of every 3 individuals with PWS are more than 200% of their ideal body weight, and some have even experienced stomach ruptures from overconsumption.⁷⁶ The metabolic physiology of PWS differs from obesity in normal individuals, such as increased ratio of adiposity to lean mass,⁸¹ decreased total and resting energy expenditure,⁸ and 4 times greater fasting ghrelin levels.³³ PWS is a difficult to treat syndrome that has not benefited from the most radical medical and surgical interventions. Bariatric surgery, in particular, has been applied toward PWS with limited effectiveness and concerning safety profiles given the increased overall medical comorbidity in this population.⁶⁹

Individuals with PWS consume more food and for longer periods of time than other obese individuals, suggesting a disruption of basic satiety mechanisms and a dysfunctional reward system.⁴⁸ These disruptions have a basis in manifesting as postmeal hyperactivation of specific brain regions involved in the food satiety and reward circuitry, including the hypothalamus, NAc, amygdala, hippocampus, medial prefrontal cortex, orbitofrontal cortex, and insula.^{35,56,73} In functional MRI studies comparing individuals with PWS to obese and healthy-weight controls, individuals with PWS demonstrated higher activity in reward/limbic regions and lower activity in the hypothalamus before eating compared with controls. Thus, patients with PWS may be predisposed to overconsumption due to abnormal basal activity in these brain regions.³⁷

PWS represents the pathological intersection between reward and satiety circuitry in the human brain that drives uncontrolled feeding behavior and leads to extreme obese states. Targeting this obese subgroup of individuals may be a reasonable first approach to neuromodulation for obesity given the well-known medical refractoriness of this population.³⁶ Clinical trials targeting the LH are underway for these patients, and future trials of NAc DBS are planned. Specifically, the LH has already been targeted via DBS for obesity⁹⁰ and headache,³⁹ and the NAc for OCD, anxiety, addiction, and depression.⁴⁹ We propose that these same targets may be potential targets for DBS in PWS (Fig. 1).³⁶

Discussion

Despite the success of bariatric surgery in the treatment of obesity, there still exists a significant proportion of patients who fail surgical therapy. A neural basis for overeating exhibited in obese patients has been elucidated by both functional imaging as well as DBS studies in animals and limited DBS experience in human patients as well. Specifically, both the hypothalamus (feeding and satiety) and the NAc (reward) have been identified as crucial regulators of food eating behavior that have been demonstrated to be responsive to DBS in treating obesity in animals models. Although upfront costs of DBS are nearly twice that of bariatric surgery, similar degrees of cost savings and cost effectiveness noted in bariatric surgery can likely be obtained with DBS as long as its treatment effects endure, and especially if it is used as an adjunct to bariatric surgery in those patients who experience weight regain.

These patients in whom bariatric surgery ultimately fails likely represent a subpopulation of morbidly obese individuals with a psychiatric basis for their continued excessive food consumption that could lend itself to DBS

therapy. Patients with PWS may represent an additional treatment indication for DBS given the overlap between the obesity secondary to hyperphagia and the dysregulated reward circuitry observed in this disorder that may make them ideal candidates for DBS. Finally, the efficacy of DBS for obesity will have to be definitively evaluated with a clinical trial that will benefit most from stringent and thoughtful inclusion criteria.

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