

Morally Justifiable Surgical Placebo-Controlled Trials for Deep Brain Stimulation in the Management of Chronic Treatment Resistant Anorexia Nervosa

Lipsman et al. present promising data concerning Deep Brain Stimulation (DBS) in the management of chronic, treatment-resistant anorexia nervosa (AN).(1) They conclude with a call for a placebo-controlled, randomised trial in this context.

Randomized, double-blind placebo-controlled studies are the gold standard of evidence-based medicine, allowing researchers to control for the placebo effect and researcher bias. However, Surgical Placebo-Controlled Trials (SPTs) are controversial. Critics object that SPTs may deprive patients of effective treatment, and undermine patient–doctor trust.(2) Furthermore, participants in the placebo arm of a SPT of DBS might be exposed to the perioperative risks of haemorrhage and infection, without the possibility of benefiting from the putative active component of the intervention under investigation.

Despite these criticisms, one of us has argued elsewhere that SPTs can be permissible if they meet five essential criteria:

1. Clinical equipoise
2. Preliminary evidence that the procedure results in a significant improvement, and that there may be a placebo/ nocebo effect or bias.
3. The risks are minimized, and unnecessary harms are avoided.
4. No deception.
5. The research question is clinically important and will potentially result in a significant difference to clinical practice.(3)

These criteria could potentially be met by an SPT of DBS for AN. First, Lipsman et al. provides preliminary evidence that DBS may result in significant improvement in AN. However, there is a paucity of evidence concerning the use of DBS in the

management of AN. In view of this, the severity of AN, and the lack of effective treatment alternatives, such a trial could meet criteria (1) and (5). With respect to (2), evidence from a placebo-controlled trial of DBS for treatment-resistant depression raises the possibility that the observed improvements might be attributable to a placebo effect.(4) Third, a robust informed consent process could ensure that subjects do not participate under the therapeutic misconception. This would help ensure that an SPT of DBS in AN could meet criteria (3); we note that this may be particularly challenging in this vulnerable population. Finally, with respect to (4) it is impossible to carry out a SPT of DBS in the absence of *any* risk. However, a well-designed trial could minimize risk to an *acceptable* level, when the risk of the sham intervention is understood in the context of the high mortality risk of individuals who suffer from AN. Moreover, if the SPT established that active DBS is effective, then active stimulation could subsequently be offered to participants in the placebo arm.

One might still object those in the placebo arm are exposed to the risks of surgery, with no possibility of benefit, and that true equipoise thus does not exist. However, elsewhere we have argued that active stimulation itself might be associated with harmful psychological side effects, possibly compromising autonomy and authenticity.(5) Those subjected to active stimulation may therefore risk further harms to the placebo group. It is thus essential that any future trial measures not only effects on eating, but also evaluates potential harmful effects on personality, authenticity and autonomy.

1. Lipsman N, Lam E, Volpini M, Sutandar K, Twose R, Giacobbe P, et al. Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. *Lancet Psychiatry* [Internet]. [cited 2017 Feb 24]; Available from: <http://www.sciencedirect.com/science/article/pii/S2215036617300767>
2. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med*. 1999 Sep 23;341(13):992–6.
3. Savulescu J, Wartolowska K, Carr A. Randomised placebo-controlled trials of surgery: ethical analysis and guidelines. *J Med Ethics*. 2016 Dec 1;42(12):776–83.
4. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the

Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. *Biol Psychiatry*. 2015 Aug 15;78(4):240–8.

5. Maslen H, Pugh J, Savulescu J. The Ethics of Deep Brain Stimulation for the Treatment of Anorexia Nervosa. *Neuroethics*. 2015;8(3):215–230.