

## Short Communication

# Exploratory meta-analysis on deep brain stimulation in treatment-resistant depression

Smith DF. Exploratory meta-analysis on deep brain stimulation in treatment-resistant depression.

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**Objective:** Deep brain stimulation is currently an experimental treatment for major depressive disorder. Information is lacking, however, on how sham responding may affect efficacy. This article applies exploratory meta-analysis to address that topic.

**Methods:** Data on benefits of deep brain electrical stimulation come from a recent review. Stimulated brain regions included subgenual cingulate, capsular interna, nucleus accumbens, and medial forebrain bundle. Expert opinion plus random number software was used to generate hypothetical values for sham responding.

**Results:** An effect size of 1.71 (95% CI: 1.47–1.96) was obtained for deep brain stimulation versus sham treatment in patients suffering from long-term treatment-resistant depression.

**Conclusion:** Preliminary findings on deep brain electrical stimulation suggest that the procedure may be 71% more effective than sham treatment. Expressing these findings as patients-needed-to-treat, deep brain electrical stimulation is required by 2.9 patients with long-term treatment-resistant depression in order for one of them to benefit.

Keywords: affective disorder; deep brain stimulation; depression; treatment resistance

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### Significant outcomes

- This exploratory meta-analysis showed a statistically significant effect in favour of deep brain stimulation in treatment-resistant major depressive disorder.
- In terms of patients-needed-to-treat, the results show that one out of three patients with long-term treatment-resistant depression can be expected to benefit from deep brain electrical stimulation.

### Limitation

- Estimates of sham responding to deep brain stimulation are derived by expert opinion rather than by properly controlled clinical trials.

### Introduction

Direct electrical stimulation in the brain continues to attract much attention for relief of treatment-resistant

depression (1,2). There is, however, still great uncertainty concerning efficacy, due in part to lack of information on sham responding to the intensive selection and surgical procedures (3). In the absence

Table 1. Summary of data used for an exploratory meta-analysis on benefit of deep brain electrical stimulation in patients with long-term treatment-resistant depression

Study (Reference number)	Anatomical site	Number of patients	Responders (%)	Random estimate of sham response (%)	Estimate of effect size	Estimate of 95% CI
Kennedy et al. (11)	Subgenual cingulate	20	55	14	2.02	1.89–2.14
Puigdemont et al. (12)	Subgenual cingulate	8	62.5	18	2.03	1.92–2.14
Holtzheimer et al. (13)	Subgenual cingulate	10	43	10	1.92	1.76–2.07
Lozano et al. (14)	Subgenual cingulate	21	29	18	0.62	0.50–0.74
Malone (6)	Anterior limb of capsula interna	17	53	14	1.94	1.81–2.06
Dougherty et al. (15)	Anterior limb of capsula interna	30	21	15	0.41	0.27–0.55
Bewernick et al. (16)	Nucleus accumbens septi	13	45	11	1.89	1.75–2.03
Schlaepfer et al. (17)	Supero-lateral branch of the medical forebrain bundle	6	85	23	2.94	2.81–3.08

The information in the first three columns is summarised from a very recent review (2). The estimates of sham response were obtained by expert opinion plus random number software (<http://www.random.org/integers/>) (see 'Materials and methods' section).

of such information, we cannot establish the likelihood of success of the intervention. There are, however, ways of estimating the likelihood of sham responding in certain situations (4). Here, expert opinion is applied to gain an understanding of the potential role of sham responding in the efficacy of deep brain stimulation in patients suffering from long-term treatment-resistant depression.

### Materials and methods

Information on the likelihood of sham responding in patients with long-term treatment-resistant depression was solicited from three eminent colleagues (Helen Mayberg, Donald A. Malone Jr., and Thomas E. Schlaepfer) with extended experience using deep brain stimulation for psychiatric disorders (5–7). The information that they supplied along with the present authors' understanding of treatment-resistant depression (8) placed the likelihood of sham responding in the range 10–25%. Using random number software (<http://www.random.org/integers/>), nine values were generated and were applied consecutively to the data provided by a recent review on deep brain stimulation in long-term treatment-resistant depression (Table 1) (2).

### Results

Effect sizes were too heterogeneous to uphold a fixed effects model ( $Q = 36.2$ ,  $df = 7$ ,  $p < 0.01$ ) (9). Therefore, a random effects model was used, and it provided an estimate of effect size of 1.71 (95% CI: 1.47–1.96;  $Z = 13.6$ ,  $df = 7$ ,  $p < 0.01$ ) for deep brain stimulation versus sham treatment in patients with long-term treatment-resistant depression. In the present context, an effect size of 1.71 means that deep brain stimulation was 71% more likely than

sham treatment to be of benefit for patients with long-term treatment-resistant depression.

### Discussion

The present exploratory finding can be expressed in terms of patients-needed-to-treat (10). Assuming a sham response rate of 20% to the intensive selection and surgical procedures required by deep brain stimulation, then we can expect 2 out of 10 patients to report some benefit even in the absence of electrical stimulation. The estimate of effect size derived by the present exploratory meta-analysis indicates that, in addition to sham responding, another 1.4 patients (i.e. sham response  $\times 0.71$ ) can be expected to benefit from electrical stimulation. Thus, for every 2.9 patients (10/3.4) with long-term treatment-resistant depression receiving deep brain electrical stimulation, one can be expected to benefit. Whether this level for patients-needed-to-treat is viewed as large or small is, of course, a matter of opinion.

A shortcoming of the present analysis relates to the current lack of empirical evidence on the level of sham responding to deep brain non-stimulation in patients with long-term treatment-resistant depression. Information on that topic can be expected to come eventually from properly controlled, large-scale clinical trials that either disprove or confirm the present findings. One reviewer of this article noted that two presentations at recent conferences concerned as yet unpublished accounts on clinical trials on deep brain stimulation that were discontinued owing to no difference between active versus sham treatment in depressed subjects. Be that as it may, at least 10 additional clinical trials on deep brain stimulation in depressed subjects are currently underway, according to records available at [clinicaltrials.gov](http://clinicaltrials.gov). Perhaps the outcome of those studies, once published, can provide further insight concerning the ultimate value of sham

versus active deep brain stimulation in treatment-resistant depression.

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