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Deep Brain Stimulation for Treatment-Resistant Depression: Preliminary Evidence Review

Health Quality Ontario

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Conflict of Interest Statement

All reports prepared by HQO are impartial. There are no competing interests or conflicts of interest to declare.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by HQO and its partners, the Ontario Health Technology Advisory Committee (OHTAC) — a standing advisory sub-committee of the HQO Board — makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Rapid reviews, as well as evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the HQO website. Visit http://www.hqontario.ca for more information.

About Preliminary Evidence Reviews

Preliminary evidence reviews summarize existing evidence and information about health services and technologies that Health Quality Ontario and the Ontario Health Technology Advisory Committee (OHTAC) have been asked to review, but for which there is insufficient evidence available to conduct a full evidence-based analysis. In each instance, OHTAC will have determined that a full review is not possible. In some instances, OHTAC may wish to make recommendations based on the information available in the preliminary evidence review.

About Health Quality Ontario Publications

To conduct its preliminary evidence reviews, HQO and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, HQO collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This preliminary evidence review is the work of HQO's Evidence Development and Standards branch or one of its research partners, and the Ontario Health Technology Advisory Committee of HQO, and developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a preliminary evidence review, it may not reflect all scientific research available. Additionally, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature review specified in the methods section, if available. This preliminary evidence review may be superseded by an updated publication on the same topic. Please check the HQO website for a list of all publications: http://www.hqontario.ca/en/mas/mas_ohtas_mn.html.

Table of Contents

List of Abbreviations

ATHF	Antidepressant Treatment History Form
BP	Bipolar disease
CGI	Clinical Global Impression scale
CGI-S	Clinical Global Impression-Severity scale
DBS	Deep brain stimulation
ECT	Electroconvulsive therapy
GAF	Global Assessment of Functioning scale
HDRS	Hamilton Depression Rating Scale
HRQOL	Health-related quality of life
ITT	Intent-to-treat
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
NAcc	Nucleus accumbens
OCD	Obsessive-compulsive disorder
RCT	Randomized controlled trial
RESP50	≥ 50% change in HDRS score from baseline
SCC	Subcallosal cingulate
SCG	Subcallosal cingulated gyrus
SD	Standard deviation
TRD	Treatment-resistant depression
VC/VS	Ventral capsule / ventral striatum

Executive Summary

Objective

Health Quality Ontario was asked to review the evidence on deep brain stimulation (DBS) for treatment-resistant depression (TRD) and to examine whether it is clinically effective as both a short-term and long-term (e.g., 3 to 5 years) treatment.

Clinical Need: Condition and Target Population

TRD occurs in approximately 10% to 20% of patients who are depressed despite the use of adequate courses of conventional approaches such as antidepressant drugs, psychotherapy, and electroconvulsive therapy (ECT). (1) Estimates of TRD have also been reported to be 20% to 30% and as high as 60%, depending on its definition. Without successful treatment, ongoing depressive symptoms may lead to functional impairment, increased use of health care resources, suicide, and increased risk of death from other causes. Risk factors for depression include a history of mental illness in family members, a previous episode of depression, traumatic life events, difficult relationships, poor housing or other socioeconomic factors, workplace-related and other stress, and a history of multiple chronic conditions (e.g., stroke, heart disease, obesity, cancer, AIDS) and the medications used to treat these conditions.

Technology

Deep brain stimulation is a nonpharmacological treatment for TRD that involves focal stimulation at a specific neuroanatomic target such as the subcallosal cingulate white matter, the ventral caudate/ventral striatum, or the nucleus accumbens. The treatment requires surgical implantation of unilateral or bilateral electrodes and a neurostimulator permanently implanted in the subclavicular area. Electrical stimulation is transmitted from the stimulator to the leads, which are connected to each other by an extension that runs under the scalp and skin of the neck. Advantages of DBS are its reversibility and the ability to telemetrically and noninvasively adjust stimulation variables to maximize benefits and minimize side effects.

Research Question

What is the clinical effectiveness of deep brain stimulation versus no DBS (i.e., usual care) for treatment-resistant depression?

Research Methods

Literature Search

Search Strategy

A literature search was performed on October 15, 2012, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid EMBASE, PsycInfo, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2010, until October 15, 2012. Appendix 1 provides details of the literature search. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full reports
- Published between January 1, 2010, and October 15, 2012
- Randomized controlled trials, health technology assessments, systematic reviews, and meta-analyses
- Clinical studies that included ≥ 6 subjects
- Adults aged ≥ 18 years

Exclusion Criteria

- Animal studies

Outcomes of Interest

- Depression severity
- Response rate / response to therapy (symptom based, using RESP50)
- Remission (symptom based)
- Adverse events (e.g., device, medical, cognitive, neuropsychological)

Quality of Evidence

The quality of the body of evidence for each outcome is examined according to the GRADE Working Group criteria. The overall quality is determined to be very low, low, moderate, or high using a step-wise, structural methodology.

As stated by the GRADE Working Group, the overall quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate – the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited – the true effect may be substantially different from the estimate of the effect
Very Low	Very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of effect

Summary of Findings

Future investigations of the clinical effectiveness and safety of this surgical intervention are warranted in this severely disabled population who have exhausted other therapeutic options. For the outcomes investigated:

Depression Severity

- Based on very low quality of evidence, patients show an improvement in depression severity after DBS therapy.

Overall Response (Response to Therapy)

- Based on very low quality of evidence, approximately 50% of patients respond to DBS therapy.

Complete Response (Remission)

- Based on very low quality of evidence, approximately one-third of patients enter remission after DBS therapy.

Adverse Events

- Based on very low quality of evidence, 3 of 7 studies reported patient suicide (the most serious, nonreversible adverse event) after DBS therapy.

Background

Objective of Analysis

Health Quality Ontario was asked to review the evidence on deep brain stimulation (DBS) for treatment-resistant depression (TRD) and to examine whether it is clinically effective as both a short-term and long-term (e.g., 3 to 5 years) treatment.

Clinical Need and Target Population

TRD occurs in approximately 10% to 20% of patients who are depressed despite the use of adequate courses of conventional approaches such as antidepressant drugs, psychotherapy, and electroconvulsive therapy (ECT). (1) Estimates of TRD have also been reported to be 20% to 30% and as high as 60%, depending on its definition. (2) The European Union's Committee for Human Proprietary Medicinal Products defines TRD as the failure of consecutive treatments with 2 products of different classes, used for a sufficient length of time at an adequate dose, to induce an acceptable effect in patients. (3) For antidepressant drug therapy, an adequate trial is indicated by a score of 3 or higher on assessment using the Antidepressant Treatment History Form (ATHF). (4)

The 2002 Mental Health and Well-Being Survey of the Canadian Community Health Survey (CCHS, Cycle 1.2) showed that 4.8% of the Canadian population age 15 years and older reported symptoms in the previous 12 months that met criteria for major depression. (5) In the same survey, 12.2% of Canadians reported having symptoms that met criteria for depression at some point over their lifetimes.

Risk factors for depression include a history of mental illness in family members, a previous episode of depression, traumatic life events, difficult relationships, poor housing or other socio-economic factors, workplace-related and other stress, and a history of multiple chronic conditions (e.g., stroke, heart disease, obesity, cancer, AIDS) and the medications used to treat these conditions. (5)

Five or more symptoms of depression lasting more than 2 to 3 weeks are considered clinically relevant, with symptoms including feelings of sadness and loss, guilt and worthlessness, loss of interest in usually-enjoyed activities, lack of interest in sex, thoughts of suicide, constipation, anxiety, feeling tired, lack of motivation, difficulties thinking or concentrating, and changes in weight, appetite, or sleep. (5) The severity of symptoms is typically rated using the Hamilton Depression Rating Scale (HDRS), also known as the Hamilton Rating Scale for Depression (HRSD or HAM-D). Different versions of the scale include HDRS-17, HDRS-24, and HDRS-28. Based on the HDRS-17, a score of 0 to 7 is considered to be within the normal range (or indicates clinical remission) and a score of ≥ 20 indicates moderate depression; however the exact score varies by the HDRS scale used. (6)

The ultimate goal of treatment is remission of symptoms, which was achieved in 67% of patients in one trial using 4 acute treatment steps. (7) Without successful treatment, ongoing depressive symptoms may lead to functional impairment, increased use of health care resources, suicide, and increased risk of death from other causes. (8)

Technology

Deep brain stimulation is a nonpharmacological treatment for TRD that involves focal stimulation at a specific neuroanatomic target such as the subcallosal cingulate white matter, the ventral caudate/ventral striatum, or the nucleus accumbens. (9) The treatment requires surgical implantation of unilateral or

bilateral electrodes and a neurostimulator permanently implanted in the subclavicular area. (10) Electrical stimulation is transmitted from the stimulator to the leads, which are connected to each other by an extension that runs under the scalp and skin of the neck. Advantages of DBS are its reversibility and the ability to telemetrically and noninvasively adjust stimulation variables to maximize benefits and minimize side effects. (11;12)

Regulatory Status

According to the Medical Devices Active License Listing by Health Canada, 2 companies are listed to provide DBS devices and accessories in Canada: Medtronic, Inc. and Advanced Neuromodulation Systems, Inc. (13) None of the licenses listed by Medtronic, Inc. are specifically for TRD. (Personal communication, Colin Foster, November 1, 2012) Similarly, the licenses listed by Advanced Neuromodulation Systems, Inc. (now, St. Jude Medical, Inc.) are indicated for nonrelevant conditions (e.g., spinal cord injury) but not for TRD. (Personal communication, Kevin Wilson, October 29, 2012) However, St. Jude Medical, Inc. is conducting research in Canada on DBS in TRD.

Ontario Context

Currently in Ontario, DBS is not covered for TRD, and a physician cost for the procedure in this province is not known. There is a surgical fee for the insertion of electrodes but not for the indication of TRD, and codes exist for clinical programming of DBS electrodes but with no associated clinical condition specified. The procedure is not in use and/or not insured in Alberta, Manitoba, Saskatchewan, Nova Scotia, New Brunswick, Newfoundland and Labrador, and Prince Edward Island. Coverage status is unclear or unknown for British Columbia, Quebec, Northwest Territories, Yukon, and Nunavut.

Preliminary Evidence Review

Research Question

What is the clinical effectiveness of deep brain stimulation versus no DBS (i.e., usual care) for treatment-resistant depression?

Research Methods

Literature Search

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Outcomes of Interest

- Depression severity
- Response rate / response to therapy (symptom based, using RESP50)
- Remission (symptom based)
- Adverse events (e.g., device, medical, cognitive, neuropsychological)

Quality of Evidence

The quality of the body of evidence for each outcome is examined according to the GRADE Working Group criteria. (14) The overall quality is determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual confounding factors. (14) For more detailed information, please refer to the latest series of GRADE articles. (14)

As stated by the GRADE Working Group, the overall quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to that of the estimate of the effect
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Very Low	Very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of effect

Results of Literature Search

The database search yielded 297 citations published between January 1, 2010, and October 15, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Seventeen studies (9 systematic reviews and 8 clinical studies) met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand searched to identify any additional potentially relevant studies.

For each included study, the study design was identified and is summarized below in Table 1, which uses a modified version of Goodman's hierarchy of study design. (15)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	-
Large RCT	-
Small RCT	-
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	-
Non-RCT with noncontemporaneous controls	-
Systematic review of non-RCTs with historical controls	9[a]
Non-RCT with historical controls	8[a]
Database, registry, or cross-sectional study	-
Case series	-
Retrospective review, modelling	-
Studies presented at an international conference	-
Expert opinion	-
Total	**17**

Abbreviation: RCT, randomized controlled trial.
[a]Before-and-after type clinical studies.

Systematic Reviews

Nine systematic reviews were identified and the details of those studies are shown in Appendix 3, Table A2. All systematic reviews were qualitative in nature. Case studies of less than 5 patients included in the systematic reviews were excluded in the following discussion. All studies in these systematic reviews showed heterogeneity in the brain targets studied, sample sizes, and lengths of follow-up.

Al-Harbi et al (16) examined neuromodulation therapies for TRD. The literature search was conducted between 2000 and 2012 and included clinical trials, open clinical studies, case series, systematic reviews, and meta-analyses. Six studies were considered eligible based on the inclusion criteria. Sample sizes ranged from 6 to 59 patients. Length of follow-up was not consistently reported. The authors concluded that DBS is safe and effective but noted that future research is needed on efficacy, side effects, and cost-effectiveness in larger TRD populations. (16)

Al-Harbi (17) examined the therapeutic options for TRD. The literature search was conducted between 1990 and 2011, and only original studies, clinical trials, systematic reviews, and meta-analyses were included. Two clinical studies were identified for inclusion, with the sample size of only 1 of the studies reported (n = 21). Length of follow-up ranged from 1 to 6 years. Overall, beneficial effects of DBS were reported, and the authors concluded that DBS is safe and effective but suggested that further randomized clinical trials are needed in the future. (17)

Schlaepfer et al (18) examined TRD and disease awareness, treatment goals, treatment strategies, and future plans for the treatment of TRD. There were no date limits to the literature search, and 4 relevant studies were reviewed on clinical effectiveness of DBS. Sample sizes were not clear. The length of follow-up ranged from 6 months to 1 year. Overall, the authors reported beneficial effects of DBS and limited side effects. (18)

Rizvi et al (19) examined the clinical and preclinical evidence on vagus nerve stimulation and deep brain stimulation for TRD. The literature search dates were not provided. Clinical trials and case studies pertaining to human and animal subjects were included. Excluding the case studies, 7 relevant studies on the clinical effectiveness of DBS were reviewed. Their sample sizes ranged from 6 to 21 patients with follow-up ranging from 1 month to 3 years. The review authors concluded that DBS has beneficial antidepressant effects and that randomized controlled trials are needed to confirm its efficacy. (19)

Sarnecki et al (20) examined clinical studies on DBS for TRD in unipolar depressed patients. The literature search was current as of March 2010, and case studies were excluded. Among the clinical studies identified for inclusion, sample sizes ranged from 3 to 20 patients and length of follow-up ranged from 5 weeks to 6 months. The authors report on 5 clinical studies but list 6 clinical studies in their summary tables. This systematic review analyzed the data from 5 clinical studies in aggregate and did not provide a detailed description of the analysis. The authors used the Oxford Quality Scoring System to critically appraise 6 studies and found that studies did not use an established randomization method; that although studies employed blinding, either single or double, the details were not provided; and that there was a mix of reporting and description of drop-outs. The authors concluded that the results of DBS for TRD are promising but also noted study limitations including small sample sizes, a lack of long-term follow-up, no information on relapses, a failure to fully consider a placebo effect, lack of consideration of co-morbid conditions, and lack of double-blinding. (20)

Andrade et al (21) examined nonpharmacological treatments for major depressive disorder (MDD). Literature search dates were not provided, and articles and textbooks were eligible. Articles were excluded "due to data repetition" or if they lacked clinical outcome information. Eleven studies were included; however 7 studies had sample sizes less than 5. The remaining 4 studies had sample sizes of 6 to 20 patients and follow-up ranging from 6 months to 4 years. The authors concluded that DBS shows positive outcomes and minimal side effects; however, more detailed descriptions of study methods are needed. (21)

Lakhan et al (22) examined DBS for TRD and obsessive-compulsive disorder (OCD). Following a literature search current as of May 2009 and restricted to human studies, clinical studies, and reviews, the authors identified 7 clinical studies that included only patients with TRD and 1 study that included patients with both TRD and OCD. Among the 7 clinical studies on TRD, sample sizes ranged from 1 to 21 patients and follow-up ranged from 1 week to 24 months. Studies were critically appraised. The authors highlighted the unique qualities of these clinical studies: the patient was used as his/her own control; single- and/or double-blinding was considered to have been achieved by periods of active stimulation and zero voltage (e.g., sham or off stimulation); randomization refers to random selection of ordering of active/sham stimulation periods; and using the patient as his/her own control reduces the

placebo effect. The authors concluded that DBS is promising and that current study shortcomings are anticipated to be addressed in the near future. (22)

Kuhn et al (23) examined DBS for psychiatric disorders including obsessive-compulsive disorder, Tourette syndrome, and depression. The literature search was conducted for the period 1980 to January 2009. Studies were eligible if they involved at least 3 patients. Relevant to DBS and depressive disorder, four studies were included: 1 study had a sample size of 3 and the others ranged from 6 to 20 patients. Length of follow-up ranged from 6 months to 1 year. Overall, the authors concluded that DBS is promising although long-term data on adverse events are needed and, to date, there are no definite conclusions. (23)

Shelton et al (24) examined therapeutic strategies for TRD. The literature search covered January 1990 to November 2009, although the types of eligible studies were not specified. The authors described 3 studies, with sample sizes ranging from 6 to 23 patients and a high length of follow-up (mean of 14.4 years). The authors concluded that DBS was efficacious in small studies but other therapeutic approaches should also be considered. (24)

Clinical Studies

Eight clinical studies were identified, and the details of those studies are shown in Appendix 3, Tables A3 and A4. A number of the clinical studies summarized here, grouped by length of follow-up for the outcome measures of response to therapy and/or remission, were included in the systematic reviews described above. Our descriptive assessment of the evidence from these studies follows this summary.

Response to therapy is defined as ≥ 50% decrease in depression severity score from baseline (RESP50). This measure is typically expressed as a percentage of patients who respond to DBS therapy. Remission is defined as a depression severity score within the accepted normal range and is similarly expressed as a percentage of patients who have achieved remission after DBS therapy. (6;25)

Length of Follow-up: Up to 1 Year

A clinical study conducted in Germany by Bewernick et al (26) examined the long-term effects of DBS applied to the nucleus accumbens in 11 TRD patients. According to an earlier publication by the same author, patients were recruited from their treating psychiatrist, media ads, or a university hospital outpatient clinic. (27) Patients were included if they were diagnosed with major depressive disorder, unipolar type, and were in a current episode. Other inclusion criteria were HDRS-28 ≥ 21 and failure to respond to adequate trials of primary antidepressants, ECT, and psychotherapy. The primary outcomes were antidepressant response measured by the HDRS-28 (RESP50) and remission (HDRS-28 score < 10) at 12 months of follow-up. Secondary outcomes included clinical effects, health-related quality of life (HRQOL), cognition, and safety. The length of follow-up for the entire study was up to 4 years. Analyses were performed as intent-to-treat. Last observation carried forward and imputing missing values was employed although the details are not clear. Reasons for losses to follow-up were not described, except for 1 patient who committed suicide during the 12 months of follow-up. (26)

A prospective open-label trial by Lozano et al (28), conducted across 3 Canadian centres, examined the efficacy of DBS applied to the subcallosal cingulate gyrus in 21 TRD patients. Patients were recruited from the University of British Columbia, McGill University, and the University Health Network in Toronto. Patients were eligible if they had been diagnosed with major depressive disorder, were in a current episode, had a HDRS-17 score ≥ 20, and had failed to respond to standard therapies (e.g., antidepressants, ECT). The primary outcome was RESP50 based on HDRS-17, which was administered by the treating psychiatrist at baseline, 3 months, 6 months, and 12 months. The secondary outcome was depression severity as measured by the Clinical Global Impression-Severity scale (CGI-S). One patient

was lost to follow-up due to suicide. This multicentre study was an extension of previous work by the same group of researchers; that work was single-centred and included a separate sample of TRD patients. (28)

A clinical study by Puigdemont et al (29) conducted in Spain examined short- and long-term clinical outcomes and patients' tolerance of DBS applied to the subgenual cingulated gyrus in 8 TRD patients. Patients were recruited from a hospital and were eligible if they were diagnosed with major depressive disorder, had a HDRS-17 score of ≥ 18, and had previously received and failed other therapies (e.g., antidepressants, ECT). The primary outcome was performance on HDRS-17, and RESP50 and remission were calculated. HDRS was assessed at least twice a month for 12 months. Secondary outcomes were performance on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression scale (CGI). Cognitive functioning was also measured. Last observation carried forward was applied for missing data. (29)

Bewernick et al (27) conducted a clinical study in Germany that examined DBS applied to the nucleus accumbens in 10 TRD patients. Patients were recruited from their treating psychiatrist, media ads, or the University hospital outpatient clinic. Patients were included if they were diagnosed with major depressive disorder, unipolar type, were in a current episode, had a HDRS-28 ≥ 21, and failed to respond to adequate trials of antidepressants, ECT, and psychotherapy. The primary outcome was RESP50 and remission at 12 months postsurgery. Secondary outcomes included additional depression scales, a measure for anxiety, and neuropsychological assessment. Data were analyzed as last observation carried forward and missing values were calculated by averaging the 2 preceding and following values. Losses to follow-up included early terminators (n = 1) or patients with less than 12 months of follow-up (n = 2). Data were ascertained at various time points but the long-term effects for the patient population reflect 12 months of follow-up. (27)

In an extension of previous clinical studies in Germany (27;30), Grubert et al (31) examined DBS applied to the nucleus accumbens in 10 patients with TRD and impairments in cognitive function. Thirteen cognitive tests were assessed at baseline and at 1 year. The sample size was reduced for some of the tests, although an explanation was not provided. (31)

Length of Follow-up: > 1 Year

A longitudinal study conducted by Holtzheimer et al (32) in the United States examined the efficacy and safety of DBS applied to the subcallosal cingulate in 17 TRD patients. The study design included phases of sham stimulation (lead-in and discontinuation, both single-blinded) and active simulation (24-weeks and long-term, both open-label). Due to patient safety concerns, the discontinuation phase was eliminated. Both sham stimulation phases included patients being told they were being randomized to receive either active or sham stimulation, although in reality all patients received some periods of sham stimulation. Patients were recruited through a university website and regional psychiatrists and were eligible if they were diagnosed with major depressive disorder or bipolar disease (BP), in a current episode, had failed to respond to at least 4 antidepressant treatments (scoring ≥ 3 on the Antidepressant Treatment History Form), had shown failure or intolerance to ECT, and had HDRS-17 ≥ 20 at screening. The primary outcomes were RESP50 measured by HDRS-17 and remission defined as HDRS-17 < 8, both considered primary endpoints when ascertained after 24 weeks of active stimulation. The secondary endpoints were response and remission ascertained at 1 and 2 years after active stimulation. Adverse events were defined as an undesired change in physical or mental status or in relevant laboratory measures warranting clinical assessment and/or intervention (e.g., infection, headache, nausea, suicidal ideation, malfunction of the device). Serious adverse events were defined as an event that resulted in death, permanent loss of biological function, and/or the need for hospitalization or prolongation of hospitalization (e.g., infection, suicidal ideation or attempt). Reasons for losses to follow-up were not described in detail, except for the description of 1 patient who left the study due to a lack of efficacy. (32)

A clinical study by Kennedy et al (33) conducted in Canada examined the long-term effectiveness and safety of DBS applied to the subcallosal cingulate gyrus in 20 TRD patients. This study is an extension and long-term follow-up of previous work. (1;34;34) Patients, recruited from the hospital setting and referred by hospital and community psychiatrists, were eligible if they were diagnosed with major depressive disorder, were in a current episode, had documented nonresponse to at least 4 adequate treatment trials (e.g., pharmacotherapy, ECT, psychotherapy), and had a HDRS-17 $\geq$ 20. The primary outcome was RESP50 measured by the HDRS-17. Secondary outcomes were remission, the absolute change in HDRS-17, and change in HRQOL. Analyses were performed as observed-case analysis and intent-to-treat analysis. The length of follow-up was 3 to 6 years, with a mean of 3.5 years. Reasons for lack of follow-up included removal of DBS device (n = 2), suicide (n = 1), unconfirmed suicide (n = 1), lost to follow-up (n = 1), cancer death (n = 1), and lack of efficacy (n = 1). For 2 patients, the reason for lack of follow-up was unknown. (33)

A multicentre clinical study by Malone et al (35;36) conducted in the United States examined long-term outcomes of DBS applied to the ventral anterior internal capsule/ventral striatum in 17 TRD patients and 1 with bipolar disorder. Patients were referred for recruitment by treating psychiatrists from 3 centres and were eligible if they were diagnosed with chronic or recurrent depression with 2 or more years in the current episode, previous treatment attempts including antidepressants, ECT, and psychotherapy, and a HDRS-24 $\geq$ 21. The primary outcome was depressive symptoms measured by the HDRS (RESP50 and remission). The secondary outcomes were depressive symptoms and functional outcomes measured by MADRS and the Global Assessment of Functioning scale (GAF), respectively. Cognition was also assessed. Data were collected at baseline (presurgery) and monthly thereafter. Analysis included last observation carried forward when data were available 1 month previously. All patients were followed for at least 6 months and up to approximately 4 years (the mean was about 2 years), with last follow-up time points varying due to staggered enrolment. The authors concluded that there were no withdrawals from the original study of 15 patients. (35;36)

Descriptive Assessment

Due to the lack of a comparator group, a formal meta-analysis was not performed. Available data from individual studies were assessed qualitatively for 4 outcome measures: depression severity, response to therapy, remission, and adverse events. Details of the results for these outcome measures are shown in Appendix 3, Table A4.

Depression Severity

Depression severity was examined in 7 studies using the HDRS as a continuous measure. A variety of HDRS scales were used: 4 studies used HDRS-17, (28;29;32;33) 1 study used HDRS-24, (36) and 2 studies used HDRS-28. (26;27) Four of the 7 studies compared baseline HDRS scores to scores at follow-up and all showed a statistically significant decrease in HDRS scores. (26;27;29;33) The remaining 3 studies suggested that DBS had a beneficial effect on HDRS scores. (28;32;36)

Response to Therapy and Remission

Studies with information on response to therapy and remission at 1 year were examined and are shown in Table 2.

Table 2: Proportion of Patients Classified as Responders to Therapy or in Remission at 1 Year After DBS Therapy

Responders to Therapy			
Author, Year	%	Site	Analysis
Bewernick et al, 2012 (26)	45.5	NAcc	ITT
Lozano et al, 2012 (28)	29.0	SCG	No ITT
Holtzheimer et al, 2012 (32)	36.0	SCC	No ITT
Puigdemont et al, 2012 (29)	62.5	SCG	ITT
Kennedy et al, 2011 (33)	55.0	SCG	ITT
Bewernick et al, 2010 (27)	50.0	NAcc	No ITT
Remission			
Author, Year	%	Site	Analysis
Bewernick et al 2012 (26)	9.1[a]	NAcc	ITT
Holtzheimer et al, 2012 (32)	36.0	SCG	No ITT
Puigdemont et al, 2012 (29)	50.0	SCG	ITT
Kennedy et al, 2011 (33)	20.0	SCG	ITT

Abbreviations: ITT, intent-to-treat; NAcc, nucleus accumbens; SCC, subcallosal cingulate; SCG, subcallosal cingulated gyrus.
[a]Calculated based on report of 1 patient in stable remission.

Individual studies reported on response to therapy (also referred to as *overall response*) and/or remission (*complete response*). Using 1 year of follow-up as an arbitrary cut-point for which there was relatively consistent information reported, the proportion of patients who responded to therapy—defined as ≥ 50% decrease in HDRS from baseline—ranged from 29% to 62.5% based on 6 studies (Table 2). For those studies that used an ITT analysis, the proportion of patients who responded to therapy ranged from 45.5% to 62.5%. For remission, the proportion of patients who achieved a low HDRS score (below a pre-specified HDRS cut-point, in the range of what is generally accepted as normal or non-clinical depression) ranged widely, from 9.1% to 50%, based on 4 studies and also for those studies that used an ITT analysis. The wide range of remission proportions may be related to the length of the current episode of depression, as patients having longer episodes are less likely to remit. (7;12) In Bewernick et al (26) patients had a mean length of their current diagnosis of MDD of approximately 9 years, compared to roughly 6 to 7 years in Puigdemont et al (29) and Kennedy et al. (33)

When all 7 clinical studies with relevant outcome information were reviewed in aggregate—including the differing brain target sites, analytic methods, and lengths of follow-up—the proportion of patients who responded to therapy ranged from 29% to 92% and the proportion of patients in remission ranges from 9.1% to 58%. For only those studies that used an ITT analysis, the proportion of patients who responded to therapy ranged from 45% to 87.5% and the proportion of patients in remission ranges from 9.1% to 50%. Table 3 provides a summary of the range of values, means, and medians for these data. The maximum proportion of patients who responded to therapy is considerably higher than the values shown in Table 2—as high as 92%. One factor to consider is that the study that contributed this high value included patients whose current MDD episode had lasted 2 years, a relatively low duration compared to the other studies. Other reasons for these differences are discussed below (see "Summary of the Preliminary Evidence Review").

Table 3: Proportion of Patients Classified as Responders to Therapy or in Remission After DBS Therapy

Responders To Therapy				
Study Characteristics (Number)	Min %	Max %	Mean %	Median %
ITT: 1 year of follow-up (n=3)	45.5	62.5	54.3	55.0
ITT: all time points (n=3)	45.5	87.5	58.6	55.0
All studies (n=7)	29.0	92.0	53.1	50.0
Remission				
Study Characteristics (Number)	Min %	Max %	Mean %	Median %
ITT: 1 year of follow-up (n=3)	9.1[a]	50.0	26.4	20.0
ITT: all time points (n=3)	9.1[a]	50.0	30.2	35.0
All studies (n=5)	9.1[a]	58.0	31.0	35.0

Abbreviations: ITT, intent-to-treat analysis; Max, maximum; Min, minimum.
[a]Calculated based on report of one patient in stable remission.

When only those studies that used a homogeneous population of TRD patients were examined by brain target site for the proportion of responders and of those in remission, using all follow-up data, the median proportions were similar across brain target sites and in comparison with values obtained when the data were examined in different ways (Tables 2 and 3). The median proportion of responders was 47.8% for the nucleus accumbens and 55% for the subcallosal cingulated gyrus. The median proportion of patients in remission was 9.1% for the nucleus accumbens and 36.3% for the subcallosal cingulated gyrus. Only 1 study contributed to the proportion of patients in remission for the nucleus accumbens and therefore the value is skewed lower. (Table 4)

Table 4: Proportion of Patients Classified as Responders to Therapy or in Remission After DBS Therapy, by Brain Target Site

Responders To Therapy					
Author, Year	Brain Site	Min %	Max %	Median %	AEs
Bewernick et al, 2012 (26)	NAcc	45.5	50.0	47.8	1 suicide
Bewernick et al, 2010 (27)	NAcc				–
Lozano et al, 2012 (28)	SCG				1 suicide
Puidgemont et al, 2012 (29)	SCG	29.0	87.5	55.0	–
Kennedy et al, 2011 (33)	SCG				–
Remission					
Author, Year	Brain Site	Min %	Max %	Median	AEs
Bewernick et al, 2012 (26)	NAcc	9.1[a]	9.1[a]	9.1[a]	1 suicide
Puidgemont et al, 2012 (29)	SCG	20.0	37.5	36.3	–
Kennedy et al, 2011 (33)	SCG				–

Abbreviations: AEs, adverse events; NAcc, nucleus accumbens; SCG, subcallosal cingulated gyrus.
[a]Calculated based on report of 1 patient in stable remission.

Adverse Events

Adverse events were reported in 7 studies. The most serious and non-reversible adverse event is suicide, which was reported in 3 of 7 studies. (26-28) None of the studies found adverse effects on cognitive

function, and in 6 studies cognitive function was reported to be stable or improved over time. (26;27;29;31;32;36)

Other Relevant Studies

A horizon scan conducted by the Agency for Healthcare Research and Quality (AHRQ) in 2012 concluded that, as a treatment for major depressive disorder and OCD, DBS had a moderately high potential impact, with a beneficial effect on the health care system but a limited effect overall due to a small target population and barriers to acceptance. (37)

The Medical Advisory Secretariat of Ontario's Ministry of Health and Long-Term Care conducted an evidence-based analysis (EBA) in 2005 on the use of DBS for Parkinson disease and other movement disorders. The literature search was conducted from 2001 onwards. The primary focus of the EBA was on motor function, with the following outcome measures examined: motor function and tremor, activities of daily living, percentage of the day spent with motor dysfunction, and L-dopa equivalent daily dosage. (38)

AHRQ conducted a 2011 comparative effectiveness review on nonpharmacologic interventions for treatment-resistant depression in adults. However, it focused on technologies other than DBS such as repetitive transcranial magnetic stimulation (rTMS). (39)

In addition, we identified 2 relevant randomized clinical trials, 1 discontinued and 1 ongoing. A trial in the United States, sponsored by Medtronic, has been stopped early because it failed to show a significant difference at 16 weeks. (Personal communication, Kitty Zanata, November 2, 2012) This was a multicentre, double-blind, sham-controlled, parallel randomized clinical trial, with an anticipated study completion date of October 2014. The objective was to examine whether bilateral DBS is safe and effective. The primary outcome was depressive symptoms at 16 weeks and the secondary outcomes were quality of life (also at 16 weeks) and adverse events (long-term follow-up). The study planned to enrol 30 patients and the design included a 16-week blinded treatment phase where patients received either active DBS or sham stimulation (control group). The study was to be expanded to 200 patients across 20 sites. All patients were to receive active stimulation after the blinded phase. Length of follow-up was 12 months, with long-term follow-up anticipated for the study of potential adverse events. Inclusion criteria were patients with a diagnosis of major depressive disorder who had tried at least 4 different treatments (e.g., antidepressant medications, combinations of antidepressant medications, and/or electroconvulsive therapy). (40)

A multicentre, randomized, double-blind, sham-controlled clinical trial is currently underway in Germany, with an estimated study completion date of September 2013. The objective is to examine whether DBS applied to the cingulate cortex is safe and effective. The primary outcome is depression score and the secondary outcomes are biological. The length of follow-up is 4 weeks to assess primary and secondary outcomes. The study will enrol 20 patients who have been diagnosed with a major depressive episode and have not had an acceptable clinical response due to failure with at least 3 antidepressant treatments. Additional inclusion criteria are patients with a HDRS > 20. (41)

Summary of the Preliminary Evidence Review

In aggregate, the evidence suggests a beneficial effect of DBS for treatment of TRD. However, the lack of rigorous study designs impedes the ability to make strong conclusions. Some methodological concerns include:

- Lack of an adequate comparator group. In the RCT context, this may take the form of a parallel design in which the comparator group is no DBS. The current body of literature uses the before-and-after study design without a parallel comparator group. Without a parallel comparator group, differences across time may confound the results.
- Addressing the placebo effect. Authors have argued that a placebo response, in which the insertion of the DBS device itself leads to improvements in depressive symptoms, is highly unlikely given the severe refractory state of depression in TRD patients and the observation of sustained responses. (35) When the placebo response is examined, only 10% of patients show a placebo response. (35) In the RCT context, the placebo response may be addressed by what is referred to as sham stimulation, the insertion of the DBS device but without brain stimulation. However, careful study design is needed as patients tend not to tolerate the off phases and depressive symptoms can worsen. (27)
- Lack of randomization. Studies need to address potential confounding variables such as medication, psychotherapy, premorbid functioning, psychosocial support, and personality/ temperament. (32) A number of these factors were addressed by strict inclusion and exclusion criteria, but only randomization can address the unknown potential confounding factors. Further to the inclusion/exclusion criteria, a homogeneous TRD patient population would be ideal, whereas some of the studies also included bipolar patients.
- Lack of blinding. Due to the nature of the DBS device, it is not possible to employ double-blinding. Some studies have altered DBS parameter settings intraoperatively, (1) and consequently some studies have been interpreted as using the blinding methodology. (20) However, this approach is not able to provide the rigorous information necessary to determine the long-term effectiveness of DBS on clinical outcomes.
- Small sample sizes. Given the prevalence of MDD, it is not clear why the studies were small ($\leq$ 21 patients), including the recently terminated RCT by Medtronic. (40)

Quality of Evidence

Overall, the GRADE assessment of the quality of evidence by outcome is very low, as shown in Appendix 2, Table A1. For individual studies, the risk of bias was assessed and is shown in Appendix 3, Table A5.

Overall Summary

Future investigations of the clinical effectiveness and safety of this surgical intervention are warranted in this severely disabled population who have exhausted other therapeutic options. (42)

Conclusions

Depression Severity

- Based on very low quality of evidence, patients show an improvement in depression severity after DBS therapy.

Overall Response (Response to Therapy)

- Based on very low quality of evidence, approximately 50% of patients respond to DBS therapy.

Complete Response (Remission)

- Based on very low quality of evidence, approximately one-third of patients enter remission after DBS therapy.

Adverse Events

- Based on very low quality of evidence, 3 of 7 studies reported patient suicide (the most serious, non-reversible adverse event) after DBS therapy.

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Appendices

Appendix 1: Literature Search Strategies

Literature Search – Deep Brain Stimulation

Search date: October 15, 2012
Databases searched: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; PsycInfo; Cochrane Library; Centre for Reviews and Dissemination (CRD)

Limits: 2010-current; English

Database: Ovid MEDLINE(R) <1946 to October Week 1 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 12, 2012>, Embase <1980 to 2012 Week 41>
Search Strategy:

#	Searches	Results
1	Deep Brain Stimulation/	23064
2	deep brain stimulat*.ti,ab.	11082
3	or/1-2	25468
4	exp *Depressive Disorder/ use mesz	56588
5	Depressive Disorder, Major/ use mesz	16328
6	exp *depression/ use emez	146223
7	Depressive Disorder, Treatment-Resistant/ use mesz	68
8	treatment resistant depression/ use emez	187
9	(depressi* adj2 (treatment adj resist*)).ti,ab.	2450
10	depression.ti.	135328
11	or/4-10	253223
12	3 and 11	914
13	limit 12 to english language	824
14	limit 13 to yr="2010-Current"	339
15	remove duplicates from 14	275

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Deep Brain Stimulation] this term only	131
#2	deep brain stimulat*:ti,ab,kw (Word variations have been searched)	238
#3	#1 or #2	238
#4	MeSH descriptor: [Depressive Disorder] explode all trees	6547

#5	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only	5
#6	depressi*:ti (Word variations have been searched)	11528
#6	depressi*:ti (Word variations have been searched)	11528
#7	#4 or #5 or #6	14132
#8	#3 and #7 from 2010 to 2012	4

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR deep brain stimulation	24
2	(deep brain stimulat*):TI	35
3	#1 OR #2	38
4	MeSH DESCRIPTOR depressive disorder, treatment-resistant	0
5	MeSH DESCRIPTOR depressive disorder EXPLODE ALL TREES	697
6	((depressi* adj2 (treatment adj resist*))):TI	1
7	(depressi*):TI	811
8	#5 OR #6 OR #7	986
9	#3 AND #8	1
10	(#9):TI FROM 2010 TO 2012	1

1 result is Spanish, therefore excluded

PsycINFO 2002 to October Week 2 2012

#	Searches	Results
1	deep brain stimulation/	887
2	deep brain stimulat*.ti,ab.	1544
3	or/1-2	1586
4	major depression/	44425
5	"depression (emotion)"/	3818
6	treatment resistant depression/	840
7	(depressi* adj2 (treatment adj resist*)).ti,ab.	728
8	depression.ti.	25648
9	or/4-8	51068
10	3 and 9	155
11	limit 10 to yr="2010 -Current"	75
12	Limit 11 to English language	71

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile – Based on Qualitative Assessment

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Depression severity (HDRS – continuous)							
7 (observational)	Very serious limitations (-2)[a]	No serious limitations	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Undetected	n/a	⊕ Very low
Response (HDRS – categorical)							
7 (observational)	Very serious limitations (-2)[a]	No serious limitations	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Undetected	n/a	⊕ Very low
Remission (HDRS – categorical)							
5 (observational)	Very serious limitations (-2)[a]	No serious limitations	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Undetected	n/a	⊕ Very low
Adverse effects							
7 (observational)	Very serious limitations (-2)[a]	No serious limitations	Serious limitations (-1)[b]	Serious limitations (-1)[c]	Undetected	n/a	⊕ Very low

Abbreviations: HDRS, Hamilton Depression Rating Scale.
[a]Lack of randomization and lack of blinding during the follow-up phase.
[b]Patients with bipolar disease in 2 studies. (32;36)
[c]Based on small sample sizes.

Appendix 3: Summary Tables

Table A2: Summary of Included Systematic Reviews (N=9 Studies)

Author, Year	Number of Included Studies	Description of Included Studies	Results[a]	Adverse Effects
Al-Harbi et al, 2012 (16)	6[b]	MC; otherwise not specified	RESP50: 36–92% RESP50: 57% at 1 mo, 48% at 6 mo, 29% at 12 mo; ↓ depressive symptoms associated with ↓ disease severity	DBS remains safe and effective
Al-Harbi, 2012 (17)	2[c]	MC pilot study; follow-up study; otherwise not specified	RESP50: 57% at 1 mo, 48% at 6 mo, 29% at 12 mo; ↓ depressive symptoms associated with ↓ disease severity	DBS remains safe and effective
Schlaepfer et al, 2012 (18)	4[d]	Small studies; otherwise not specified	RESP50: 40–60% at 6 mo, 50% at 1 yr	Safe and effective; potential side effects in PD; cognitive side effects are limited with improvements also shown
Rizvi et al, 2011 (19)	7[e]	Open-label trials	RESP50: 20–35% at 1 mo, 40–67% at 6 mo, 29–63% at 1 yr, 46% at 2 yrs, 75% at 3 yrs Remission[f]: 0–10% at 1 mo, 20–35% at 6 mo, 30–50% at 1 yr, 15% at 2 yrs, 50% at 3 yrs	Most common side effects were headaches, agitation, pain at the incision site
Sarnecki et al, 2011 (20)	5[g]	Clinical studies	RESP50: 58%, 95% CI: 44–71% (n=50 patients) Remission[h]: 26%, 95% CI: 16–40% (n=50 patients)	Adverse events ranged from swollen eyes (60% of patients in 1 study) and infections (33% of patients in 1 study) to pain (5% of patients in 1 study)
Andrade et al, 2010 (21)	4[i]	Clinical studies	RESP50: 53.3–60% Remission: 35–40% 83% of patients significantly improved without postsurgery medication	Complications ranged from pain at implantation site and technical problems to neuropsychological
Lakhan et al, 2010 (22)	3[j]	Clinical studies	RESP50: 60% (1 study) Remission: 35–66%	Minor adverse effects (e.g., skin infections and hardware erosion)
Kuhn et al, 2010 (23)	3[k]	MC pilot study	48–71% symptom reduction RESP50: 60% (1 study) Remission[l]: approx. 34%	No cognitive impairment

Table A2 (cont'd): Summary of Included Systematic Reviews (N=9 Studies)

Author, Year	Number of Included Studies	Description of Included Studies	Results[a]	Adverse Effects
Shelton et al, 2010 (24)	3[m]	Prospective study; otherwise not specified	Remission: 22–67%; 11/23 patients showed significant improvements in their depressive symptoms; 50% ↓ in depressive symptoms (or RESP50, not clear)	Neuropsychological (e.g., epilepsy, personality changes) and weight gain

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; HRSD, Hamilton Rating Scale for Depression; MC, multicentre; mo, month; PD, Parkinson's disease; RESP50, the proportion of patients who show ≥ 50% reduction in depression score from baseline for a given depression scale.
[a]Some values have been rounded to whole numbers. Where the outcome measure was not clear but response was indicated, RESP50 was assumed.
[b]Studies included: Holtzheimer (2012), Lozano (2012), Blomstedt (2011), Bewernick (2010), Malone (2009), Lozano (2008), and Mayberg (2000/2005).
[c]Studies included: Lozano (2012) and Kennedy (2011).
[d]Studies included: Bewernick (2010), Malone (2009), Lozano (2008), and Mayberg (2005).
[e]Studies included: Kennedy (2011), Lozano (2011), Bewernick (2010), Puigdemont (2011), Malone (2009), Lozano (2008), and Mayberg (2005), excluding case reports in narrative review.
[f]Remission based on scale used: HRSD-28 ≤ 10, HRSD-24 ≤ 10, HRSD-17 ≤ 7.
[g]Studies included: Bewernick (2010), Malone (2010), Malone (2009), Lozano (2008), and Mayberg (2005), excluding study by Schlaepfer (2007) with n=3.
[h]Remission defined as a HDRS of ≤ 8.
[i]Studies included: Malone (2009), Lozano (2008), Mayberg (2005), and Health (1979), excluding case studies of < 6 patients.
[j]Studies included: Malone (2009), Lozano (2008), and Mayberg (2005), excluding case studies of < 6 patients and 1 study with no outcome information.
[k]Studies included: Malone (2009), Lozano (2008), and Mayberg (2005), excluding 1 study of < 6 patients.
[l]Remission defined as a HAM-D of ≤ 8 or ≤ 7.
[m]Studies included: Bewernick (2009), Sachdev (2005), and Mayberg (2005), excluding 1 case study of < 6 patients.

Table A3: Summary of Study Characteristics (N=8 Studies)

Author, Year	Study Location	Population	Study Design	Brain Target	Length of Follow-up (Length of Intervention)	Sample Size	Losses to Follow-up[a]
Bewernick et al, 2012 (26)	Outpatient clinics, Germany	TRD	Before-After	NAcc	Up to 4 yrs	11	6 (55%)
Lozano et al, 2012 (28)	University, outpatient clinics, MC, Canada	TRD	Before-After	SCG	Up to 1 yr	21	1 (5%)
Holtzheimer et al, 2012 (32)	Outpatient clinic, Atlanta, USA	TRD + BP	Sham-Active	SCC	Up to 2 yrs	17[b]	6 (35%)
Puigdemont et al, 2012 (29)	Hospital, Spain	TRD	Before-After	SCG	Up to 1 yr	8	0 (0%)
Grubert et al, 2011 (31)	Outpatient clinics, Germany	TRD	Before-After	NAcc	1 yr	10	3 (30%)
Kennedy et al, 2011 (33)	Outpatient clinics, Canada	TRD	Before-After	SCG	Up to 6 yrs[c]	20	9 (45%)
Bewernick et al, 2010 (27)	Outpatient clinics, Germany	TRD	Before-After	NAcc	1 yr	10	3 (30%)
Malone et al, 2010[d] (36)	Outpatient clinics, MC, USA	TRD + BP	Before-After	VC/VS	Up to 4 yrs[e]	17[b]	–[f]

Abbreviations: BP, bipolar; MC, multicentre; NAcc, nucleus accumbens; SCC, subcallosal cingulated; SCG, subcallosal cingulated gyrus; TRD, treatment-resistant depression; VC/VS, ventral internal capsule/ventral striatum; yr, year.

[a]Maximum losses to follow-up at the end of the end of the study period. Some values have been rounded to whole numbers.

[b]n=7 patients had a diagnosis of bipolar disease (32) and n=1 patient had a diagnosis of bipolar disease (36).

[c]Mean length of follow-up of 3.5 years.

[d]Study details based on original report of n=15 patients (35).

[e]Mean length of follow-up of 1.96 years.

[f]Losses to follow-up reported in original study (n=11/15 at 12 months of follow-up) but unclear in the current 2010 paper.

Table A4: Detailed Summary of Study Design Characteristics and Results (N=8 Studies)

Author, Year	Study Population	Description of Intervention	Results	Other Comments
Bewernick et al, 2012 (26)	11 patients, aged 32–65 yrs, dx MDD, unipolar type, in current episode	Bilateral DBS, Medtronic model 3387, NAcc	Baseline, mean age: 48.4 yrs (SD: 11.1) 33% female Baseline, mean ATHF[a]: 3.18 (SD: 0.40) Baseline, mean HDRS-28: 32.2 (SD: 5.5) 1-yr HDRS-28: 20.2 (SD: 7.5) ($P < 0.005$)[b] 2-yr HDRS-28: 19.5 (SD: 9) ($P < 0.01$) LFU HDRS-28: 22.1 (SD: 13.4) ($P < 0.05$) 1-yr RESP50[c]: 45.5% 1-yr remission[d]: 9.1% Significant ↓ in mean HDRS-28 in short- and long-term ($P < 0.05$ across yrs 1, 2 and LFU) Predominately no changes in cognitive function at follow-up (2–3 yrs, LFU), $P > 0.05$ Adverse effects (events, n): surgical, 15 (e.g., swollen eyes); parameter change, 26 (e.g., anxiety); unrelated to DBS, 18 (e.g., fractures), [n=59 total events] 1 attempted suicide, 1 committed suicide at 12 mos	Additional outcome measures included MADRS, HAMA, HRQOL (SF-36), Hautzinger list of positive activities, NP; ITT analysis
Lozano et al, 2012 (28)	21 patients, aged 30-60 yrs, dx MDD, single or recurrent episode, in current episode	Bilateral DBS, Libra device, SCG	Baseline, mean age: 47.3 yrs (SD: 6.1) 61.9% female Baseline, mean ATHF: not reported[e] Baseline, mean HRDS-17: 27.6 (SD: 4.5) 1-mo RESP50: 57% 6-mo RESP50: 48% 1-yr RESP50: 29% Reductions in depressive symptoms associated with improvements in disease severity and global patient improvement Adverse effects (top 3 events, n): GI, 15; musculoskeletal, 12; skin, 9 [n=68 total events] 1 attempted suicide, 1 committed suicide at 8 wks	No reported ITT analysis

Table A4 (cont'd): Detailed Summary of Study Design Characteristics and Results (N=8 Studies)

Author, Year	Study Population	Description of Intervention	Results	Other Comments
Holtzheimer et al, 2012 (32)	17 patients, aged 18-70 yrs, dx MDD or BP, in current episode	Bilateral DBS, Libra device, SCC	Baseline, mean age: 42 yrs (SD: 8.9) Baseline, mean age, MDD: 40 yrs (SD: 9.3) 59% female, 70% in MDD patients Baseline, mean HDRS-17: 23.9 (SE: 0.7), n=17, n=10 MDD 24-wk mean HDRS-17: 13.1 (SE: 1.5), n=16, n=10 MDD 1-yr mean HDRS-17: 13.6 (SE: 2.1), n=14, n=9 MDD 2-yr mean HDRS-17: 7.3 (SE: 0.7), n=11, n=8 MDD 24-wk RESP50: 41% (n=17) 1-yr RESP50: 36% (n=14) 2-yr RESP50: 92% (n=12) 24-wk remission[f]: 18% (n=17) 1-yr remission: 36% (n=14) 2-yr remission: 58% (n=12) Adverse effects (top 3 events, n): nausea, 5; headache, 3; hand numbness/tingling, 2; infection, 2 [n=22 total events]; 6 related to device/surgery Serious adverse effects (top 3 events, n): anxiety, 5; infection, 2; suicidal ideation, 2; suicide attempt, 2 [n=12 total events]; 2 related to device/surgery	10 MDD patients, 7 BP patients; 1 BP patient accounted for 9 of the 12 serious adverse effects; NP function improved or was stable over time; additional information for BDI, GAF; no reported ITT analysis
Puigdemont et al, 2012 (29)	8 patients, aged 18–70 yrs, dx MDD	Bilateral DBS, Medtronic model 3387, SCG	Baseline, mean age: 47.4 yrs (SD: 11.3) 75% female Baseline, mean HDRS-17: 21.3 (SD: 2.4) 6-mo RESP50: 88% 1-yr RESP50: 63% 6-mo remission[g]: 38% 1-yr remission: 50% HDRS-17 significantly improved ($P < 0.001$) Adverse effects: n=2, cephalalgia; n=3, neck pain; n=1, attempted suicide	Only study to have the DBS pulse-generating device implanted abdominally; additional information on MADRS, CGI; NP unaffected by DBS; acute changes in single-blinded stimulation; few adverse effects; ITT implemented (but not reported)

Table A4 (cont'd): Detailed Summary of Study Design Characteristics and Results (N=8 Studies)

Author, Year	Study Population	Description of Intervention	Results	Other Comments
Grubert et al, 2011 (31)	10 patients, aged 32–65 yrs, dx MDD, unipolar type, in current episode	Bilateral DBS, Medtronic model 3387, NAcc	Baseline, mean age: 48.6 yrs (SD: 11.7) 40% female Baseline, mean ATHF[a]: 3.2 (SD: 0.42) Baseline, mean HDRS-28: 32.5 (SD: 5.3) Significant ↑ in attention (P = 0.001), learning and memory (P = 0.010 to 0.038), executive function (P = 0.015), visual perception (P = 0.035)	Influence of predictor variables and z scores also examined; adverse effects not reported; no ITT analysis reported
Kennedy et al, 2011 (33)	20 patients, dx MDD, in current episode	Bilateral DBS, Medtronic 3387, SCG	Baseline, mean age: 47.4 yrs (SD: 10.4) 55% female Baseline, mean HDRS-17: 24.4 (SD: 3.5) 1-yr RESP50[h]: 55% 2-yr RESP50: 45% 3-yr RESP50: 60% LFU RESP50: 55% 1-yr remission[i]: 20% 2-yr remission: 20% 3-yr remission: 40% LFU remission: 35% HDRS-17 significantly ↓ at LFU (P < 0.001) Adverse effects: n=6 psychiatric (e.g., suicidal ideation); n=6 nonpsychiatric (e.g., knee replacement, pancreatitis) [n=12 total, 8 patients]	Additional information on work and medication status, HRQOL (SF-36); remission was considered a secondary outcome in this study only; ITT analysis
Bewernick et al, 2010 (27)	10 patients, aged 32–65 yrs, dx MDD, unipolar type, in current episode	Bilateral DBS, Medtronic 3387, NAcc	Baseline, mean age: 48.6 yrs (SD: 11.7) 40% female Baseline, mean ATHF: 3.2 (0.4) Baseline, mean HDRS-28: 32.5 1-yr RESP50: 50% Remission[j] (lasting 1 mo): n=3 patients Mean total HDRS-28 significantly improved at all time points Adverse effects: n=12 surgical (e.g., pain, swollen eye); n=24 parameter change (e.g., headache); n=12 unrelated (e.g., cancer, gastritis, suicides) [n=48 total] 1 attempted suicide, 1 committed suicide	Additional information on MADRS, HAMA, BDI, symptoms, positive activities by Hautzinger, NP; no detrimental effect on NP testing; no ITT analysis

Table A4 (cont'd): Detailed Summary of Study Design Characteristics and Results (N=8 Studies)

Author, Year	Study Population	Description of Intervention	Results	Other Comments
Malone et al, 2010[k,l] (36)	17 patients (n=15 patients[k]), aged 18–55 yrs, chronic or recurrent depression, in current episode	Bilateral DBS, Medtronic 3387 (13 of 15 patients), VC/VS	Baseline, mean age: 46.3 yrs (SD: 10.8)[k] Baseline, mean HDRS-24: 33.1 (SD: 5.5)[k] 3-mo RESP50: 47%[k] 6-mo RESP50: 40%[k] LFU RESP50: 53%[k] 3-mo remission: 20%[k,m] 6-mo remission: 20%[k] LFU remission: 40%[k] Improvements in HDRS from baseline to 12 mo, mean decrease: 14.4 (SD: 2.0)[k] Serious adverse effects related to surgical implantation (e.g., infection) and stimulation-induced acute effects (e.g., paresthesias, anxiety)[l] Serious adverse effects: n=25[k]	1 BP patient; additional information on MADRS, GAF; no deleterious effects on NP tests; suicidality (44%)[k]; no ITT analysis reported

Abbreviations: ATHF, Antidepressant Treatment History Form; BDI, Beck Depression Inventory; BP, bipolar patient; CGI, Clinical Global Impression Scale; DBS, deep brain stimulation; dx, diagnosis; GAF, Global Assessment of Function Scale; GI, gastrointestinal; HAMA, Hamilton Anxiety Scale; HRSD-17, 17-item Hamilton Rating Scale for Depression; HRQOL, health-related quality of life; HDRS, Hamilton Depression Rating Scale; ITT, intent-to-treat; LFU, last follow-up; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; mo, month; NAcc, nucleus accumbens; NP, neuropsychological; RESP50, ≥ 50% change in HDRS score from baseline; SCC, subcallosal cingulate; SCG, subcallosal cingulated gyrus; SD, standard deviation; SE, standard error; SF-36, 36-item Short-Form Health Survey Questionnaire; TRD, treatment-resistant depression; VC/VS, ventral internal capsule/ventral striatum; wk, week; yr, year.

[a]p-value compared to baseline.
[b]Modified ATHF, 3 is the threshold for considering a trial adequate and the patient resistant to the treatment.
[c]RESP50 stable in all patients in the second year.
[d]Remission defined as HDRS ≤ 10.
[e]ATHF of 3 or 4 based on tolerability (part of inclusion criteria).
[f]Remission defined as HDRS score < 8.
[g]Remission defined as HDRS score ≤ 7.
[h]RESP50 calculated as ITT analysis.
[i]Remission defined as HDRS ≤ 7.
[j]Remission defined as HDRS ≤ 10.
[k]Results based on Malone et al., 2009 (n=15).
[l]Results based on Malone et al., 2010 (n=17).
[m]Remission defined as HDRS ≤ 10.
Some values have been rounded to whole numbers.

Table A5: Risk of Bias (N=8 Studies)

Author, Year	Allocation Concealment[a]	Blinding[b]	Complete Accounting of Patients and Outcome Events[c]	Selective Reporting Bias	Other Limitations
Bewernick et al, 2012 (26)	Limitations	Limitations	No limitations	–	–
Lozano et al, 2012 (28)	Limitations	Limitations	Limitations	–	–
Holtzheimer et al, 2012 (32)	Limitations	Limitations	Limitations	–	–
Puigdemont et al, 2012 (29)	Limitations	Limitations	No limitations	–	–
Grubert et al, 2011 (31)	Limitations	Limitations	Limitations	–	–
Kennedy et al, 2011 (33)	Limitations	Limitations	Limitations	–	–
Bewernick et al, 2010 (27)	Limitations	Limitations	Limitations	–	–
Malone et al, 2010 (36)	Limitations	Limitations	Limitations	–	–

[a]In addition to lack of randomization.
[b]Refers to double-blinding.
[c]Complete accounting of patients refers to losses to follow-up being described, and for outcome events, having performed an intent-to-treat analysis (for primary outcome).

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