Deep brain stimulation - depression and obsessive-compulsive disorder

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

METHOD OF EVIDENCE COLLECTION:

This guideline followed the standard of a systematic evidence-based review based on the Evidence-Based Medicine movement, where clinical experience is integrated with the ability to critically analyse and apply scientific information rationally, thus improving the quality of medical care. EBM uses existing and currently available scientific evidence with good internal and external validity for the application of its results in clinical practice.[1,2]

Systematic reviews are currently considered the level I of evidence for any clinical issue by systematically summarizing information on a particular topic through primary studies (clinical trials, cohort studies, case-control or cross-sectional studies) using a reproducible methodology, in addition to integrating information on effectiveness, efficiency, efficacy and safety.[1,2]

We used the structured form to formulate the question synthesized by the acronym PICO, in which the **P** corresponds to the patient with **Depression or Obsessive-Compulsive Disorder**, **I** for **Deep Brain Stimulation** intervention, **C** of comparison with **Simulation of Deep Brain Stimulation**, and **O** for the clinical **Outcome**. From the structured question we identified the descriptors that formed the basis of the search for evidence in the databases Medline-PubMed, Embase and Cochrane. Thus, 21 studies were selected, after the eligibility criteria (inclusion and exclusion), to answer the clinical question (**Annex** I).

CLINICAL QUESTION:

Can patients with depression or obsessive-compulsive disorder benefit from deep brain stimulation?

Degree of recommendation and strength of evidence:

A: Experimental or observational studies of better consistency.

B: Experimental or observational studies of lower consistency.

C: Case reports/uncontrolled studies.

D: Opinion lacking critical evaluation, based on consensus, physiological studies or animal models.

Objective:

To identify the best evidence available at the present time related to the use of deep brain stimulation in patients with depression or obsessive-compulsive disorder.

Conflict of interest:

The participants have declared no conflict of interest.

INTRODUCTION

Severe depressive disorders are the most frequent form of psychiatric illness, with a prevalence of about 15%. In most cases, the disease can be effectively treated with a combination of available drugs, such as antidepressants, and psychotherapy. In approximately 10% of cases, however, the disease becomes chronic and largely refractory. These patients are candidates for non-pharmacological measures, in particular, electroconvulsive therapy (ECT) or, in specialized centres, the vagus nerve stimulation or transcranial magnetic stimulation. ECT is effective but may have a high rate of recurrence and rejection by the patient. Deep brain stimulation could potentially open up new therapeutic opportunities as an effective long-term strategy with few adverse effects[3].

Obsessive-compulsive disorder is a relatively common psychiatric illness with a prevalence of about 2%. Clinically, it manifests itself in the form of obsessive thoughts, beginning between childhood and adulthood. There is high comorbidity with depression, but also with anxiety and personality disorders. Patients with obsessive-compulsive disorder have an imbalance in conduction of the cortico-thalamic-cortical connections, with a resulting absence of inhibition. There are deregulation of the serotonergic and dopaminergic systems. These assumptions are based on the known positive effect of selective serotonin reuptake inhibitor (SSRI), clomipramine hydrochloride and some neuroleptics. In addition to these pharmacological treatment approaches, therapeutic efficacy can be achieved with cognitive-behavioural therapy. Although 70% to 80% of obsessive-compulsive disorder patients respond well to cognitive-behavioural therapy and pharmacotherapy, the remaining patients have a serious chronic illness. These patients were previously candidates for neurosurgical procedures. Among these techniques, involving the production of irreversible lesions, is bilateral anterior capsulotomy, which had the highest success rate (over 60%). This data was obtained in longitudinal studies under uncontrolled conditions. Reports of deep brain stimulation (DBS) in the treatment of patients with refractory obsessive-compulsive disorder have been published continuously since 1999. Many of the publications are case reports[3].

Deep brain stimulation (DBS) is a reversible neurosurgical procedure that involves the implantation of electrodes in specific anatomical locations and the transmission of an electric impulse of varying intensity and frequency through these electrodes. DBS induces an electric field that alters the complex patterns of neuronal action and, therefore, modifies the activity of the neural circuits. DBS has been used for the treatment of essential refractory tremor and is approved for Parkinson's disease and dystonia. In 2009, DBS was approved for the intractable treatment of obsessive-compulsive disorder (OCD) in Europe and the USA. Since the mid-1960s, it has been observed that both acute and chronic stimulation can induce mood changes, including hypomania, dysphoria and anhedonia. A number of research groups are investigating different sites for implantation of electrodes: 1. Subgenual cingulate-Brodmann 25 (SCG 25): the essential role of the subgenual cingulate cortex has been demonstrated in normal or pathological mood attitudes. In addition, other studies have indicated an association between a clinical response to antidepressants and decreased metabolism in limbic and striatal areas (subgenual cingulate cortex, hippocampus, insula and pallidum) and increased metabolism in dorsal cortical areas (parietal, prefrontal, anterior and posterior cingulate cortex); 2. Ventral internal anterior capsule/ventral striatal (VC/VS): the dorsal and ventral prefrontal cortex were defined as dysfunctional, through neuroimaging studies, in patients with mood disorders. These regions are connections of a thalamocortical-corticostriatal circuit that also includes components of the striatum and thalamus. This target for DBS was defined following gamma-knife capsulotomy studies for obsessive-compulsive disorder (OCD). In patients with primary OCD, a significant improvement was observed in depressive symptoms, leading to the investigation of this goal in depression. Functional neuroimaging studies in individuals undergoing DBS showed activation of the ventral, striatum and thalamus pre-frontal cortex during acute stimulation of the VC/VS target; 3. Nucleus accumbens (NAC) and ventral

striatum: The ventral striatum NAC circuit has been associated with drug addiction and depression. The ventral striatum NAC receives projections mainly from the anterior cingulate cortex, the insular cortex and the orbitofrontal cortex. The NAC then projects to the dorsomedial nucleus of the thalamus through the ventral tegmental area, ventral pallidum and black substance, which in turn projects back to the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, amygdala, and hypothalamus, forming the limbic circuit of the basal ganglia; 4. Inferior thalamic peduncle (ITP): ITP is a bundle of fibres that connects the thalamus system to the orbitofrontal cortex. This system induces electrocortical synchronization and allows the inhibition of irrelevant stimuli to determine selective attention. ITP was identified as a potential target for stimulation in depression; 5. Lateral habenula (LH) has been proposed as a target for DBS, since the habenular nuclei complex projects to the locus coeruleus, frontal medial dorsal cortex, orbitofrontal cortex, insula and mesolimbic areas, and ventral tegmentum/brainstem.

The implantation of DBS electrodes and batteries is a complex neurosurgical procedure. Under stereotactic guidance, two electrodes are placed in deep structures of the brain, relative to a set of anatomical landmarks. Two programmable neurostimulators are implanted in the thoracic region under the clavicle and are connected to the corresponding electrode by extension leads under general anaesthesia. Systematic outpatient adjustment of stimulation parameters (active contacts, amplitude, duration, frequency) and frequent follow-ups are required, especially during the first 6-12 months after implantation. The rates of surgical complications are quite variable, and include intracranial haemorrhage, infections and, rarely, stroke, erosion by electrode or electrode migration. From a psychiatric point of view, there is a risk of developing symptoms of mania or hypomania, anxiety, depression or aggravation, but these symptoms are generally transient and respond to changes in stimulation parameters. Suicides were reported in patients with movement disorders and depression implanted with DBS in different targets[4].

Although deep brain stimulation (DBS) is an invasive procedure, it causes few adverse effects. The spectrum of unwanted effects can be classified into three types: the complications of surgical intervention, the purely technical problems and the adverse effects of the stimulation itself. The introduction of the electrodes may result in intracerebral haemorrhage depending on the surgeon and centre, which can be expected in 0.2% to 5% of surgeries. Intracerebral haemorrhage can lead to focal neurologic symptoms such as dysarthria, hemiparesis or aphasia, or even death. Postoperative infection by the implanted materials occurs in 2% to 25% of cases, but the risk can be greatly reduced by the perioperative administration of systemic antibiotics. Problems related to the device, such as breaking the electrode and failure of the neurostimulator, are rapidly decreasing as a result of technical advances. Undesirable effects of stimulation vary widely, depending on the anatomical target, but they are reversible upon cessation of stimulation. Symptoms related to neurological stimulation, such as dyskinesia, dysarthria, palpebral apraxia and, less often, unsteady gait, often resolve spontaneously, but may regress particularly with modulation of stimulation. Attention is being given to changes in mental state. Together with descriptions of positive effects on depression and anxiety, increased use of DBS has been accompanied by an increasing number of reports of induction of behavioural changes, depressive states, and manic states. To date, however, these undesirable effects have been systematically recorded only for interventions in the subthalamic nucleus. Over a 10-year observation period, a meta-analysis of DBS in Parkinson's disease described the following psychiatric adverse effects: depression in 2% to 4% of cases, mania in 0.9% to 1.7%, emotional changes by 0.1% to 0.2%, and suicide by 0.3% to 0.7%. Subthalamic stimulation may increase the risk of suicide. Adverse effects were, as a rule, only transient, and mostly resolved by adjustment of stimulation parameters, or tolerated by patients because of the predominantly positive effects[3].

RESULTS OF SELECTED EVIDENCES

Can patients with depression benefit from deep brain stimulation?

Patients (n: 20) with major depressive disorder (over one year) and treatment-resistant (antidepressants, psychotherapy and electroconvulsive therapy) receive DBS in subcallosal cingulate gyrus (SCG). Resistance to treatment may be defined as failure to respond to a minimum of four different treatments, including sufficient antidepressant drug therapy and duration, psychotherapy, and electroconvulsive

therapy. Psychiatric evaluations and stimulator adjustments were performed one, two, and four weeks after surgery, every two weeks, for three months, and then monthly for up to 12 months. The primary outcome was the percentage of patients achieving 50% or greater reduction in severity of depression as measured by the HRSD-17 score (defined as response), with a secondary outcome of those achieving clinical remission (defined as an HRSD-17 score of 7 or less). Under local anaesthesia, a stereotaxic system was used, with implantation of quadripolar electrodes in the subcallosal cingulate gyrus (SCG). A two-channel programmable internal pulse generator has been implanted. Patients were discharged between the 2nd and 5th postoperative days. Patients received continuous monopolar stimulation in settings ranging from 3.5 V to 5.0 V, with pulse width set at 90 microseconds and 130 Hz frequency. The mean HRSD-17 score in the patients improved significantly at all time points examined, after one month or more, relative to the baseline score. After one week of stimulation, 40% of the patients were considered responders and one patient was in remission. The response rate dropped to 30% with one patient in remission, two weeks after surgery. From two weeks to six months after surgery, a growing proportion of patients improved, when 60% of patients met the response criteria and 35% of clinical remission. At 12 months, 55% of patients responded to treatment and 35% achieved or were within 1 point of remission (score of 8 or less on the HRSD-17 scale). Of the patients who fulfilled the criteria for response at six months, 72.7% also presented criteria for response at 12 months, while 33% of the patients who were not considered responders in six months had a response in 12 months. Deep brain stimulation was associated with overall improvement in depressive symptomatology measured by mood, anxiety, somatic and subcomponents of sleep. The benefit in each of the symptom groups is associated with time after beginning of the stimulus. The maximum improvement of mood component occurred after three months. Longer times were necessary to achieve maximum improvements in anxiety, sleep, and somatic symptoms. Regarding adverse events, 20% of the patients presented infection, 5% convulsion, 20% headache or pain at the implant site, 35% of the cases did not present adverse events and there was no cognitive or hypomanic effect[5](B).

Patients (n: 15) between 18 and 55 years of age, with a history of at least five years of chronic or recurrent depression (two or more years in a current episode), defined by the application of the DSM-IV instrument, and in stable psychotropic medications for at least six weeks prior to joining the study. Patients also needed at least 21 points on a 24-point scale in the Hamilton Depression Assessment (HDRS). This threshold was chosen to allow the inclusion of patients partially responsive to the current treatment. Previous treatment attempts should have included: 1) Appropriate treatments (>6 weeks maximum recommended or tolerated dose) of primary antidepressant medications of at least three different classes; 2) Adequate tests (>4 weeks) of increase/combination of strategies using a primary antidepressant with at least two other different agents; 3) At least one adequate treatment of ECT (six or more bilateral treatments) and 4) Appropriate treatment of psychotherapy (at least 20 sessions with an experienced therapist). The electrodes were implanted bilaterally in the ventral internal anterior capsule/ventral striatal VC/VS with stereotactic technique guided by the image. Implantable neurostimulators placed bilaterally under general anaesthesia were used. Intraoperative stimulation test was performed after implantation, with the patient awake and able to answer the questions. The aim of the test was to identify the contact sites that produced acute mood enhancement and anxiety reduction without significant adverse effects. Common observations during intraoperative stimulation included acute improvement of mood, spontaneity, smiling, reduced anxiety and increased energy and consciousness. Adverse effects have occurred, such as tachycardia, increased anxiety, hot feeling/sweaty, perseverance in speech, and facial motor effects. After a postoperative recovery phase (2-4 weeks), patients underwent ambulatory stimulation for several hours during several days to establish safe and effective parameters. Once the appropriate settings were identified, the individuals entered the chronic stimulation phase. During this phase, they returned at least monthly for evaluation and classification of the device. Modifications to the stimulation settings, most commonly the pulse range or width, were allowed during this phase to mitigate adverse effects and to optimize effectiveness. Multiple instruments were selected to evaluate the results: the HDRS (primary measure), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Global Assessment of Functioning (GAF) scale. The effects

of DBS treatment were also categorically evaluated, with a defined response as a reduction of 50% of the depression rating scales in relation to the preoperative baseline of each individual patient. Remission was defined as a score of 10 or lower for both MADRS and HDRS. Response and remission rates were determined separately for each rating scale. The longest follow-up period was 51 months, with a mean follow-up of 23.5 (± 14.9) months. The accumulated treatment period was 353 months of experience with DBS patients. Antidepressant regimens remained stable throughout the first six months of stimulation in 75% of patients. The mean MADRS pre-implantation score for the subjects was 34.8±7.3; baseline in the HDRS was 33.1±5.5. The scores for both measures decreased with DBS treatment (MADRS and HDRS). The sustained reduction in score was observed over time, with good agreement between these two measures. The maximum reduction in both scales (approximately 50%) was obtained in three months and maintained for 12 months. The mean reduction of 16.6±2.2 in the MADRS score was observed (between the beginning and the treatment phase), which corresponded to a mean reduction of 46.6%. Mean points in HDRS decreased by 14.4±2.0 (41.9%). In the self-assessment, the Quick Inventory of Depressive Symptomatology SR and the Patient Global Impression of disease severity were evaluated at six months. In the questionnaire for the scores of depressive symptoms there was a significant improvement from 47.47 to 33.27 in six months ($p = 0.008$). In the Patient Global Impression of disease severity, scores improved from 5.27 to 3.87 ($p = 0.006$). After three months of stimulation, mean GAF increased from 43.4±0.7 (baseline) to 58.4±2.2, with the same level of improvement maintained for 12 months. On average, an increase of 12.9±2.0 points in GAF was observed between the beginning and the end of treatment ($p < 0.0009$). After one month of active DBS, 26.7% of the patients presented 50% or more reduction in the MADRS criterion for the clinical response, with 20% reaching the corresponding criterion in HDRS. Response and remission rates at both scales were similar over time, although slightly lower for HDRS. For the patients, the response rates at three months, six months and in the last follow-up were 53.3%, 46.7% and 53.3%, respectively, in MADRS, and 46.7%, 40% and 53.3%, respectively, on HDRS. The remission rates for MADRS were 33.3% at three months, 26.6% at six months and 33.3% at the last observation. The corresponding remission rates evaluated with HDRS were 20% at three and six months and 40% at the last follow-up. The main adverse events related to DBS were occipital pain, electrode fracture and hypomania; syncope; worsening depression; and insomnia[6] **(B)**.

Patients (n = 20) with a diagnosis of major depressive disorder [DSM-IV-TR, with current depressive episode lasting >1 year, with no documented response to at least four adequate treatment attempts (pharmacotherapy, ECT and psychotherapies), and HAM-D score ≥20] received deep brain stimulation through implantation in the subcallosal cingulate gyrus. At each annual visit, the 36-item Short-Form Health Survey (SF-36), in addition to HAM-D, was applied to patients. The primary efficacy outcome was the percentage of patients who responded during follow-up period. Secondary outcomes were the percentage of patients in remission, the absolute change in HAM-D over three years, and changes in baseline functioning in the SF-36. The mean duration of post-surgical follow-up after DBS implantation was 42.1 months. Follow-up was 841 months, or 70 patient-years. The percentage of patients responding was 62.5% after one year, 46.2% after two years, 75.0% after three years and 64.3% at the last follow-up visit. In the intention-to-treat analysis, a similar pattern of response rates was observed, with 55% at one year, 45% at two years, 60% at three years and 55% at the last follow-up visit. The majority (70%) of respondents at subsequent follow-up visits had also been responders one year before. The remission rates over time also remained the same: 18.8% after one year, 15.4% after two years, 50% after three years and 42.9% at the last follow-up visit. HAM-D scores were significantly lower than at baseline ($p<0.001$), although they did not differ significantly from scores in years 1, 2 and 3. Over three years, HAM-D scores decreased significantly ($p<0.001$) relative to the baseline score. In relation to SF-36, there was a significant effect on social functioning ($p<0.05$) and mental health ($p=0.05$) domains, as well as on the physical health dimension ($p=0.05$). During follow-up, 40% of the patients were hospitalized (psychiatric or clinical reasons not related to the procedure)[7] **(B)**.

Patients (n:11) were submitted to deep brain stimulation with implantation in the Nucleus accumbens (NAC). They were between 32 and 65 years of age, with a minimum score in 28-items HDRS (HDRS28) of 21 and a score in the Global Assessment of Functioning below 45, with at least more than four epi-

sodes of major depressive disorder (MDD) or chronic depression for more than two years; 45 years after the first episode of MDD; failure to respond to adequate treatments with primary antidepressants in at least three different classes; an attempt of adequate treatment with ECT (46 bilateral treatments); an adequate attempt of individual psychotherapy (420 sessions); no psychiatric comorbidity and drug-free or under stable drug regime for at least six weeks before the beginning of DBS. Bilateral DBS electrodes were implanted. The stimulation was permanent, starting with parameters of amplitude of 2 V, pulse width of 90 ms and frequency of 130 Hz. After an intraoperative test, the stimulation was turned off for a week to allow the tissue consolidation around the electrode edges and to control microleural effects. One week after the operation, this DBS configuration was resumed and the voltage was successively increased by 2-4 V. The stimulation parameters were held constant for approximately four weeks in order to recover the observations of the first acute and subacute effects (for example, improvement in clinical impression as assessed by HDRS). The stimulation was always bilateral and symmetrical. The optimal individual configuration of DBS was kept constant in each patient, at least one month before and during the end of follow-up. Additional pharmacological treatment was kept constant for at least six weeks, before and after surgery. The primary outcome was the response to antidepressant (reduction of 50% severity of depressive symptoms assessed by HDRS28 [28-items]) or remission (HDRS-score <10). Patients were classified as responders and non-responders with respect to their response at month 12 after surgery. Secondary outcome was MADRS and the Hamilton Anxiety Rating Scale (Hama). Of the patients, 45.5% reached the criterion of response in the first year. During the second year, the status of the response remained stable in all patients. The mean total HDRS score28 was significantly better, under stimulus, at all points in time. Responses were detected after the first month of stimulation in the sample as a whole (HDRS28 score: 32.2 [DP 5.5] at baseline, 23.2 [DP 5.6] after one month) and remained stable during the follow-up period (HDRS28-score: 20.2 [DP 7.5] after one year, 19.5 [SD 9] after two years, 22.1 [DP 13.4] at the last follow-up). Responders in 12 months remained responders at 24 months and at the last follow-up, and non-responders maintained their status respectively. Adverse events were related to the surgical procedure (edemaciate eye, dysphagia, pain), directly due to changes in parameters (erythema, transient increase in anxiety or tension, sweating within minutes to a few hours), or unrelated to DBS treatment (for example, gastritis, leg fracture, disc herniation). All side effects related to DBS treatment were transient, or could be stopped immediately, by means of parameter changes, so that patients did not experience any permanent adverse effects[8]**(B)**.

The following inclusion criteria were used: age between 18 and 70 years; depression or bipolar disorder, identified through the clinical interview structured with DSM-IV8 and confirmed by psychiatrists; current depressive episode lasting at least 12 months and not responding to at least four adequate antidepressant treatments (score 3 or higher in the history of antidepressant treatment and verified by medical records); intolerance to electroconvulsive therapy or inability to receive electroconvulsive therapy; 17-items HamiIton Depression Rating Scale (HDRS) score ≥10 of 20; preoperative HDRS score ≥20 on average between four weeks preoperatively and 30% or less than the lowest score; Global Assessment of Functioning (GAF) ≤ 11 out of 50, patients (n: 17) underwent deep brain stimulation (DBS) by stereotactic technique of subcallosal cingulate gyrus (SCG). The phases of care included preoperative evaluation for four weeks; surgery; simulated stimulation for four weeks. The patients received local or general anaesthesia, and the quadripolar DBS electrodes were implanted bilaterally. Intraoperative tests of individual contacts were performed in 70% of the patients, using parameters similar to those of chronic stimulation (130 Hz, 90-ms per pulse width, 4-8 mA, approximately 2 to 5 minutes of active stimulation in each contact). After electrode placement, an implantable generator pulse was placed in the infraclavicular region, with the patient under general anaesthesia, and connected to DBS electrodes, with active stimulation for 24 weeks. Patients were discharged after three days with the stimulator off. After surgery, patients entered a four-week simulated stimulation phase with weekly assessment. Patients were informed that they were being randomized to receive active or simulated stimulation for four weeks, but all received placebo stimulation. After these four weeks, all patients received 24 weeks of stimulation, with evaluation every one to two weeks. Chronic, bilateral, monopolar stimulation was used, with initial parameters of 130 Hz, 91-µs pulse width and 4 mA

(mA) current. There was an interruption attempt for four weeks, but because of the recurrence of depressive symptoms, it was aborted, with active stimulation and monthly assessments remaining for three months, then every three months for nine months, and then every six months. Other changes in DBS parameters were allowed during this phase. In addition, changes in medication and psychotherapy were authorized at the discretion of the study team and primary care providers of psychiatric treatment. Measures of efficacy included the HDRS score, the Beck II Depression questionnaire (BDI-II) and the GAF score. For HDRS and BDI, the higher scores indicate greater severity of depression. For GAF, lower scores indicate increased severity of symptoms or dysfunction. GAF score of 50 or lower indicates severe symptoms or psychosocial dysfunction, scores of 51-60 indicate moderate symptoms/dysfunction, 61-70 indicate mild symptoms/dysfunction, and ≥71 indicate absence or transient symptoms or minimal dysfunction. At each study visit, patients were questioned in detail about adverse events (AEs) and the Young Mania Rating scale was administered. An AE was defined as an unwanted change in physical or mental state, which justifies clinical evaluation or intervention. Severe AE was defined as an AE that resulted in death, permanent loss of biological function or the need for prolonged hospitalization. Serious AEs were characterized as probably or definitely related to surgery, DBS device or stimulation. There was significant improvement in all measures, with no clinically significant, or statistically significant differences between the bipolar disorder or depression groups. The HDRS count decreased significantly from baseline to the end of the four-week simulated stimulation phase (p=0.02). Compared with the end of the simulated phase, the reduction in HDRS score after four weeks of active stimulation did not show a significant reduction (p=0.06). Compared with baseline, the mean HDRS score decreased 43.6%, 43.0% and 70.1% by the 24th week, a year and two years of follow-up time, respectively. Remission and response were observed in 18% and 41% after 24 weeks, 36% and 36% after one year, and in 58% and 92% after two years of active stimulation. HDRS cut-off points were used to group patients in remission (HDRS <8), mild depression (HDRS between 8 and 15) or moderate to severe (HDRS> 15) at each follow-up point. All patients who reached the time point of two years were in remission or had only mild depressive symptoms. None of the patients described negative effects of acute stimulation. Adverse events occurred in 65% of the patients, with 76% with at least one severe adverse event not related to active stimulation. In the intraoperative, bleeding occurred. There were also infections and suicidal ideation during the stimulation period[9](**B**).

Inclusion criteria for patients (n: 4) undergoing deep brain stimulation were: presence of major depressive disorder, as determined by the DSM-IV Structured Clinical Interview, severe depression, with a score of at least 20 (out of 52) in the 17-item Hamilton Depression Scale (HAM-D-17); resistance to treatment, as determined by the lack of response to four different classes of antidepressants, psychotherapy or treatment with electroconvulsive therapy at an adequate dose and duration, and age between 20 and 60 years. The stereotactic intervention inserted DBS quadripolar electrodes, which were implanted bilaterally in the subcallosal cingulate gyrus (SCG). After three days the DBS electrodes were connected to the implantable pulse generator, under general anaesthesia. Patients were discharged one to two days after implantation of the pulse generator with the stimulator switched off. The optimization of the electrical stimulation parameters was performed during the first three months after the implantation of the DBS system. Monopolar stimulation was applied, with pulse width (60-450 us), frequency (2-185 Hz) and amplitude (0-10.5 V) being adjusted. In the first week, each electrode was tested for immediate effects on mood using the positive and negative affective scale (Panas) 20 and the visual analogue scale (VAS). The EVA scale was used to evaluate the following moods: sadness, happiness, anger, fear, anxiety and alertness. The optimal parameter was selected with the lowest amplitude required to produce a positive effect and the highest adverse effect threshold. During weeks 2 to 7, different stimulation frequencies (0, 5, 20, 50, 130 and 185 Hz) were randomly tested, with a pulse width frequency of 90 µs and a constant 5 V amplitude, clinical and mood responses being assessed using Panas, VAS and HAM-D-17. During weeks 8 to 11, the pulse widths were changed, keeping the frequency constant at 130 Hz. Various pulse widths were tested (0, 90, 150, 270, 450 us). For pulse widths up to 150 µs, the voltage was 5 V. At week 12, optimal stimulation parameters for each patient were selected based on the specific frequency or pulse width, which was associated with a

50% reduction in HAM-D-17 score in relation to the pre-treatment baseline, and which was associated with the maximum mood response in either instrument (VAS or Panas). For a period of six months, all patients received continuous stimulation using the stimulus parameters that were considered optimal. Clinical efficacy was assessed every two weeks using the HAM-D-17, MADRS and HAM-A instruments. All patients presented a maximal response in the happy mode (VAS-H) for longer pulse widths (270 or 450 µs) and 75% of the cases showed a 50% reduction in HAM-D-17. Of the patients, 50% reached the clinical response criterion (reduction of 50% in HAM-D-17 compared to the baseline) and 25% achieved a partial reduction response of 35% in HAM-D-17. There was no response in 25% of the cases. Anxiety, with dizziness and fainting, was the adverse event that occurred in 25% of the patients[10](B).

Patients (n: 10) between 32 and 65 years of age received DBS in the Nucleus accumbens (NAC). All met diagnostic criteria for major depressive disorder (MDD), unipolar type, and were in a current episode diagnosed with the structured clinical interview for DSM-IV (Axis I [SCID-I] and Axis II [SCID -II] disorders). The minimum score in 28 items, by the Hamilton Depression Scale (HDRS28), was 21 and the Global Assessment of Functioning was below 45. Other inclusion criteria were at least four episodes of MDD or chronic episode for more than two years, and more than five years after the first episode of MDD; failure to respond to appropriate treatments (>5 weeks at the maximum recommended or tolerated dose) of primary antidepressants of at least three different classes; lack of response to adequate treatments (more than 3 weeks at the normally recommended or maximum tolerated dose) of increasing/combining a primary antidepressant using at least two different augmentation/combination agents (lithium, T3, stimulants, neuroleptics, anticonvulsants, buspirone hydrochloride or a second primary antidepressant); appropriate ECT intervention (more than six bilateral treatments); an adequate intervention of individual psychotherapy (more than 20 sessions with an experienced psychotherapist), and absence of psychiatric comorbidity, drug-free or stable drug regimen at least six weeks prior to the beginning of treatment. Bilateral DBS electrodes were implanted using a stereotactic guide. Psychiatric assessments and adjustment of parameters were performed weekly during the first and second month after beginning of stimulation and up to half a year every two weeks. From seven months to two years, patients were monitored monthly. To capture potential effects of the surgery, patients were evaluated daily, in the week after surgery, when no stimulus occurred. The primary outcome was the antidepressants response (50% reduction in severity of depression symptoms, as assessed by HDRS28) or remission (HDRS28 score less than 10). Patients were classified as responders and non-responders with respect to their response in month 12 after surgery. Secondary outcomes included the Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAMA), Beck Depression Inventory (BDI), the self-rated inventory of depressive symptoms (IDSSR), the 90-Item Symptom Checklist (SCL-90) and the list of positive activities modified according to Hautzinger. In addition, preliminary safety information on the method of treatment was recorded. The stimulation was applied with stimulating pulse starting with parameters of amplitude of 2 V, pulse width of 90 µs and frequency of 130 Hz. After an intraoperative evaluation, stimulation was turned off to allow the consolidation of the lesions. One week after surgery, DBS was resumed and tension was successively increased from 2 to 4 V. The primary measure of effectiveness was a 50% reduction in HDRS28 (responders). Patients were classified as responders and non-responders in relation to their response to DBS at 12 months. Of the patients, 50% achieved the response. For a period of one month, 30% of patients were classified as remission (HDRS28 ≤10). The mean total HDRS28 score was significantly better under stimulation at all times. Benefits were observed after one month of stimulation throughout the sample (HDRS28 score: 32.5 at baseline, 23.8 after one month) and remained stable during the follow-up period (HDRS28 score: 20.8 after one year). Adverse effects were related to the surgical procedure (ocular oedema, dysphagia, pain), with changes in parameters (erythema, transient increase in anxiety or tension, sweating) or unrelated to DBS treatment (gastritis and fracture in the leg). All side effects related to DBS treatment were transient, or could be stopped immediately, by means of parameter changes, so that patients did not experience any permanent adverse effects. There was an adverse event of a suicide attempt, not related to DBS. Both events were not related to parameter changes. Both patients had also attempted suicide previously[11](B).

Men and women (not pregnant), aged 30 to 60 years (n: 22), diagnosed with major depressive disorder, and single or recurrent episode using the DSM-IV-TR criterion derived from Mini; first episode before the age of 35; chronic disease with current episode of ≥24 months or recurrent disease with at least a total of four episodes during life (including current episode ≥12 months); documented resistance to at least four life-depression treatments; cognitive-behavioural therapy considered effective; form of treatment in the current episode: documented resistance (there is, persistence of major depressive episode) to a minimum of three appropriate depression treatments of at least three different treatment categories (SSRIs, TCAs, other antidepressants, addition of lithium , irreversible MAO inhibitors); adequacy of treatments defined by a score of at least 4 according to the ATHF criteria in the current episode: documented resistance to ECT (at least six sessions [there is, a minimum score of 3 according to the ATHF criteria]) or <6 treatments if there is clear evidence of inability to tolerate more, or treatment refused; Global Assessment of Functioning with Score <50; Modified Mini-Mental State Examination score ≥27; on a current stable medication regimen or free of antidepressant medication ≥4 weeks. The surgery was performed by stereotactic technique, with insertion of the bilateral electrodes in the cingulate subcallosal gyrus (SCG). The stimulation parameters were chosen based on previous experience and on patients' responses to stimulation over a period of 1-2 weeks. HRSD-17 was the primary outcome, and the response was defined as a minimum 50% reduction in baseline HRSD-17 score (RESP50). The HRSD-17 score was applied at baseline and at three, six and 12 months after DBS. The proportion of patients in the RESP50 group was 57% at one month, 48% at six months and 29% at 12 months. The mean decline in the HRSD-17 score was: at two months, there was a reduction of 40.3%±29.8%. At six months, the drop was 43.3%±31.3%, and at 12 months, it was 41.4%±23.0%. Reductions in depressive symptomatology were associated with improvements in disease severity and overall improvements in patients. Suicide was the most serious adverse event not related to DBS. Nausea and vomiting occurred in 35% of patients[12](B).

Deep brain stimulation, although not yet approved by the FDA, is a reversible invasive technique involving the stereotactic implantation of electrodes powered by a pulse generator for specific dysfunctional brain regions implicated in mood disorders, Parkinson's disease, Alzheimer's disease, movement disorders and other neuropsychiatric disorders. The implant, in patients with depression of DBS electrodes in the Nucleus accumbens (NAC), determines in 12 months, in 50% of the cases, 50% reduction in the HDRS score, with a significant increase in leisure activities. However, the small sample size limits the interpretation of the results and surveys, and larger sample sizes are required. It was found that patients treated with DBS in subcallosal cingulate gyrus leads to variable response over time: 57% at one month, 48% at six months and 29% at 12 months. The response rate after 12 months of DBS increased to 62% when redefined as a reduction in the HRSD reference level of 40% or greater. In addition, the reduction in depressive symptoms was associated with an improvement in the severity of the disease in patients who responded to surgery[13](B).

The knowledge that patients with severe depression may benefit from injury neurosurgery has led to the adoption of DBS as a reversible and adaptive form of treatment. Based on the presence of neuronal dysregulation in limbic circuits and lesion positive effects, different target areas for DBS in depressive disorders have been discussed: ventral nucleus striatum accumbens; subgenual cingulate; internal globus pallidus; inferior thalamic peduncle; rostral cingulate cortex and lateral habenula. Epidemiological studies have evaluated the use of DBS in the ventral nucleus striatum accumbens and the subgenual cingulate, but only case reports are available for the inferior thalamic peduncle and the internal globus pallidus. Stimulation in the subgenual cingulate in 65% of patients with refractory depression results in symptom improvement after six months. There is an average 71% reduction in the Hamilton Depression Rating Scale score (HAM-D). No cognitive impairment detected after 12 months; and memory functions, sometimes negatively impacted by ECT, remained unchanged. After six months, there was a reduction of at least 50% on the HAM-D scale in 60% of the patients, and 35% of the patients met the criteria for remission (HAM-D-score <7). None of the patients had cognitive dysfunction. The nucleus accumbens constitutes a centre of interface between the neuronal circuits emotional, limbic and motor, being crucial in the experience of reward to hedonistic stimuli. This information stimulated the use of DBS in the nucleus with spontaneous positive effects, and within a

week the HAM-D score decreased by an average of 42%. When the stimulus was discontinued under double-blind conditions, 75% of cases deteriorated, with discontinuation of procedures. The correlation between stimulation and depression (HAM-D score) was significant ($p<0.01$), demonstrating the efficacy of stimulation in the nucleus accumbens. All patients responded to treatment without serious adverse effects. In addition to a 50% reduction in HAM-D score in 50% of the patients, there was distinct anxiolysis (measured by the Hamilton Anxiety Scale) within one year of observation. There is a report of DBS treatment in depressed patients, with target area of the internal ventral capsule/ventral striatum, obtaining a reduction in symptoms over the six-month observation period: the HAM-D score dropped by 42%[3]**(B)**.

What is the efficacy of DBS as an acute antidepressant therapy? In the largest open study reported so far, 20 patients with treatment-resistant depression were followed up for one year after surgery. Six months after surgery, 60% of the patients met the response criteria and 35% achieved remission. Improvements in depressive symptomatology remained stable for the remainder of the 12-month period, with 55% of patients meeting the response criteria. Similar results observed a response rate of 50%[14]**(B)**.

What is the efficacy of DBS as a relapse prevention therapy? Patients who had early response with DBS in the subcallosal cingulate gyrus (SCG) were more likely to maintain their response, although late responders (response after six months of DBS) were also observed. There are currently no relapse prevention studies, but anecdotal case reports suggest relapse when the device was inadvertently turned off or the battery failed, with a return to symptom improvement when the device is reactivated[14]**(B)**.

What are the adverse effects associated with DBS? Post-operative: pain or discomfort, intracranial or subcutaneous haemorrhage and infection in the intracranial or subclavian site. Emerging symptoms of hypomania have been reported in a limited number of patients, including those with and without a history of bipolar disorder. Follow-up of patients with neuropsychological tests did not reveal any evidence of cognitive impairment after 12 months of DBS in SCG. Adverse events associated with DBS for bipolar disorder, essential tremor and dystonia were reported in 10 years of experience, concluding that the prevalence of depression was lower (2% to 4%) than in patients with bipolar disorder who did not receive DBS, but whose suicide rate appears to be high compared to the general population and patients who did not receive DBS[14]**(B)**.

Can obsessive-compulsive disorder patients benefit from deep brain stimulation?

Patients (n: 4) with diagnosis of obsessive-compulsive disorder; Yale-Brown Obsessive Compulsive Scale (Y-Bocs) with a score of >25; Global Assessment of Functioning (GAF) score <44; and several failed attempts at treatment with anti-obsessive-compulsive medication at appropriate dosage and duration were subjected to deep brain stimulation (DBS). All patients had received at least four drugs with proven efficacy in the treatment of OCD (three selective serotonin reuptake inhibitors [SSRIs] and clomipramine hydrochloride). All patients received treatments lasting >12 weeks of maximum tolerated or approved doses, and all had been exposed to combinations of medications (for example, in addition to clomipramine hydrochloride or SSRI, serotonergic agent plus antipsychotic). All subjects received at least 12 weeks of cognitive-behavioural therapy (CBT) for OCD (exposure with response prevention) with no significant benefit. The primary outcomes were the Y-Bocs scale and 17 items of the Hamilton Depression Rating Scale (HAM-D). The stereotactic placement of the electrodes was at the base of the inner capsule, at its junction with the nucleus accumbens, followed by the connection to implantable pulse generators. The use of DBS was performed in three stages: 1) exploratory: stimulation combinations, establishing parameters over three to eight days, to determine the tolerability and to evaluate the acute effects; 2) double-blind controlled: 12 weeks with evaluation of stimulation effects using an on-off design; 3) open stimulation, seeking to optimize the results, adjusting the stimulation to conditions, pharmacotherapy and behavioural therapy. The main objective was to detect any evidence of potential efficacy, and whether DBS could specifically be performed compared to traditional anterior capsulotomy, for which it is a potential substitute treatment. The literature indicates that anterior capsulotomy produces a 35% improvement in OCD symptoms, and in about 45% of the patients receiving the surgery. The primary outcome used was the percentage of improvement in relation to the onset of OCD symptoms, as measured by the Y-Bocs scale, and the percentage of patients who achieved an improvement of 35% in this mea-

sure was calculated. In the exploratory phase, the side effects were more prominent in high amplitudes and monopolar configurations. Acute symptom responses were observed in 25% of the cases, with expressive high mood episode, increased activity and reduction in OCD symptoms. The elevation of mood decreased when the stimulators were turned off and returned when they were reconnected. The HAM-D score was 21 at the beginning of the study, 10 after the first day of acute testing, and 5 and 3 at the end of the next two days, when the most intense mood changes occurred. In the double-blind phase, the Y-Bocs scores at the beginning and throughout the four on-off periods demonstrate a significant clinical response in 50% of the cases. There was a clinically detectable and significant decline in OCD symptoms during the initial phase, in the ON blind period (17% improvement in Y-Bocs, with a decline of 36-30) and a clear worsening of symptoms (Y-Bocs increased to 32, HAM-D increased from 24 to 29, subjectively worse than at baseline), when moved to the subsequent OFF period. The Y-Bocs decreased more with ON stimulators (19.8%±29.8%) than with OFF (10.5%±17.8%). The HAM-D also decreased more with ON stimulation (22.5%±37.8%) than with them OFF (6.8%±16.5%). During follow-up in the open stimulation phase, 25% of the patients presented, over a period of seven months, a reduction of 36% in the Y-Bocs score (at 23), and then at 20 (44% improvement in relation to the beginning) and HAM-D decreased by 58% (to 10). The remaining patients developed discontinuity, mainly due to the association with depression, including suicide episode. Despite the concomitance with depression, there were patients with a Y-Bocs score reduced by 73%[15](B).

Diagnosis in patients (n: 10) with OCD was performed using the Structured Clinical Interview for DSM-IV, with a minimum level of severity [measured by the Yale-Brown Obsessive Compulsive (Y-Bocs) scale] of score 28. Resistance to treatment was defined as the inability to achieve significant improvement in OCD after pharmacotherapy, including adequate regimens (with equal doses or, if tolerated, beyond the maximum recommended dose) of at least three serotonin reuptake inhibitors (SRI), one of which had to be clomipramine hydrochloride. Associated SRI, neuroleptic and benzodiazepine combination treatments were required, as were a minimum of 20 behavioural therapy sessions (exposure and response prevention). All patients had chronic OCD, ranging from 11 to 39 years in duration. The initial pre-surgical severity on the Y-Bocs scale was 32 to 38. There was 80% follow-up for 36 months, and 10% of cases for 24 months, with discontinuation of stimulation in 20% of cases due to lack of appropriate therapeutic effects. The surgical target was the anterior limb of the internal capsule immediately anterior to the rostral border of the anterior commissure in the coronal plane. On the same day of the stereotactic implant, the neurostimulators were connected to the electrodes, with intraoperative DBS of 130 Hz for pulse widths of 90 and 210 μs, and to 2-6 V. The most common effects were improvement in mood and anxiety, spontaneity, expressiveness, verbal and facial fluency, along with increased alertness and heart rate. The evaluations were performed after about three weeks of postoperative recovery and then with 1, 3, 6, 16, 18, 24, 30, and 36 months of DBS. The primary outcome was the Y-Bocs. As clinical experience indicates that symptoms of depression and anxiety are associated with intractable forms of OCD that present for surgery, the Hamilton Depression Rating (HDRS)-24 scale and the Hamilton Anxiety (Hars) scale were used as secondary instruments. Overall functional status was assessed with the Global Assessment of Functioning (GAF). The mean Y-Bocs score, at the pre-implantation baseline, was 3,460, indicating severe disease. At three weeks after surgery, shortly before the start of pacing, the scores were 3,337, indicating that there is no effect of implant insertion alone. Y-Bocs scores decreased during DBS, reaching 2,237 in 36 months, with an average of 2,500±1,600 in three months. Stratifying patients by level of reduction in relation to the baseline pre-surgery Y-Bocs value (<25%, between 25% and 35%, and ≥35%), the following results were obtained: the number of responders' ≥35% Y-Bocs increased from 10% in one month to 50% in 36 months. With regard to comorbid depression and anxiety symptoms (24-item HDRS-24 and Hars) during DBS, the mean pre-surgical baseline HDRS-24 was 2,117, at three weeks post-implantation, but prior to stimulation, the scores were 1,997. The depression scores decreased to 1,477 for three months, after which it remained essentially stable. At 36 months, the HDRS-24 score was 1,547. Anxiety measured by Hars also improved over the long period of DBS. Hars scores were 1,827 at the pre-surgical baseline, decreasing to 1,317, three weeks after implantation (before the beginning of DBS). After three months of DBS, the Hars score

was 907, and at 36 months, 807. Regarding overall functioning, GAF scores improved significantly over time during DBS, from 3,667 at the pre-surgical baseline to 5,387 at 36 months. Potential complications of DBS can be separated into those related to surgical implantation, device failure and stimulation itself. Regarding the adverse effects of implantation, 10% of asymptomatic intracerebral haemorrhage, 10% of single generalized intraoperative tonic-clonic seizure after implant, and 10% of surface surgical wound infection after implantation. Regarding the adverse effects of the stimulation, transient sadness, anxiety and euphoria or vertigo. Patients also had motor effects (contralateral unilateral smile and muscular rigidity in the mandible with dysarthria). Olfactory and taste sensations, described as "chemical" or "metallic". All these adverse effects were reversed, usually within seconds and always within minutes, usually when DBS was discontinued or when parameters were changed, but sometimes spontaneously. There was no hypomania. Effects of DBS discontinuation include more depressed mood, acute worsening in OCD symptoms, with HDRS score increasing from 1,274 to 22,771 with discontinuation of DBS. Patients were monitored for suicide risk. No patient became acutely suicidal when DBS was discontinued. There were no significant declines in performance at the cognitive level of the group[16](B).

Patients (n: 5), with a mean age of 38 years old, underwent DBS placement in the anterior limb of the internal capsule and the region of the nucleus accumbens for OCD I refractory to treatment (pharmacological and cognitive behavioural). The mean duration of the disease was 17±4.1 years. The DBS electrode was placed by stereotactic in the region of the inner capsule. At about 30 days post-surgery, patients were randomized to a staged DBS activation (one month or two months). At follow-up, patients received simulated stimulation or active stimulation of DBS. Each patient was studied in two sessions (one simulated/one active or two active), and during programming sessions. The stimulation frequency was maintained constant at 135 Hz. Specific definitions for placebo, active and simulated DBS were established. Simulated and placebo responses were grouped for an analysis when comparing with active DBS. Active DBS analysis compared with simulated/placebo showed that active stimulation was significantly associated with response in all measured outcomes (p=0.001)[17](B).

Patients (n: 18) with refractory OCD were included, aged between 18 and 60 years, defined according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria, with a duration of disease of over 5 years, a Yale-Brown Obsessive Compulsive Scale (Y-Bocs) score >25 (on a scale of 0 to 40, with lower values indicating less severe symptoms), or a score >15 (on a scale of 0 to 20) with a Global Assessment of Functioning (GAF) score of <40 (on a scale of 1 to 90, with the highest scores indicating higher levels of function), and a disease severity score on Impression Clinical Global (CGI), a scale of more than 4 (on a scale of 1 to 7, with higher scores indicating greater disease severity). Additional inclusion criteria were the lack of response to drug therapy after adequate administration of at least three medications (defined as more than 12 weeks of the maximum tolerated dose): serotonin, serotonin reuptake inhibitor, clomipramine hydrochloride, increased of a period of at least one month with risperidone or pimozide and one of the following: lithium, clonazepam, buspirone hydrochloride or pindolol, lack of response to cognitive-behavioural therapy (exposure and response prevention technique) over a year of therapy, or after 20 sessions with at least two therapists; normal cognitive status (score >130 on the Mattis Dementia Rating Scale, ranging from 0 to 144, with lower scores indicating more severe dementia); normal findings in the MRI of the brain. The study had a randomized, double-blind, crossover design. Patients were divided into one of two groups: one group underwent active stimulation followed by a simulated stimulation period (the on-off group) and the other was submitted to simulated stimulation followed by an active stimulation period (the off-on group). An adverse event was classified as severe if the patient was hospitalized, if sequelae were present or if the event was considered serious. The subthalamic nucleus was the preoperative target through stereotaxia. The frequency and duration of the stimulation pulse were 130 Hz and 60 msec, respectively, with the voltage set for the individual patient. The primary outcome was the change in the Y-Bocs score at the end of each period. The Y-Bocs score was significantly lower at the end of the active stimulation (on stimulation period) than at the end of the simulated stimulation (off-stimulation period), with a mean score of 19±8 vs 28±7, P=0.01. The GAF score (where higher scores indicated higher levels of functioning) was significantly higher after active stimulation than after placebo stimulation (mean score at

the end of active stimulation, 56±14 vs 43±8, P=0.005). The CGI score (where the lowest scores indicate lower disease severity) was significantly lower at the end of the active stimulation than at the end of the stimulation simulation (P=0.008), with higher improvement during active stimulation observed in the on-off group than in the off-on group (P=0.03 for the period effect). MADRS scores, the Brief Scale for Anxiety, and the Sheehan Disability Scale at the end of active stimulation did not differ significantly from the score at the end of "simulated" stimulation. At the end of the first phase (three months after randomization), 75% of the patients had a response as measured by the Y-Bocs index and 100% showed a response after active stimulation (as measured by GAF). In addition, 62% of the patients presented an increase in the GAF score to 51 after active stimulation, compared to 12% after the simulated stimulation. Fifteen serious adverse events, of which four were related to surgery, were reported in 60% of patients. The most serious event was a cerebral parenchyma haemorrhage, resulting in permanent paralysis of a patient's finger. Seven transient motor events and psychiatric symptoms induced by stimulation occurred within the first month of stimulation, spontaneously or rapidly after adjustment of the setting. During the active stimulation period, behavioural adverse events were reported in 30% of patients[18]**(B)**.

Deep brain stimulation was used in the treatment of patients (n: 5) with a mean age of 36.8 years, mean Yale-Brown Obsessive Compulsive Scale (Y-Bocs) score of 35, mean of 17.4 years history of OCD and Global Assessment of Functioning (GAF) score between 10 and 30, diagnosed through a structured psychiatric interview according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR). In addition, the patient must have a history of OCD for more than five years and a Y-Bocs score greater than 23, which represents severe or extreme conditions. Two or more pharmacological treatments, including serotonin reuptake inhibitors, neuroleptics, anticonvulsants, benzodiazepines and cognitive-behavioural therapy, for a period of more than six months for each trial had been attempted. Despite this treatment, the reduction of scoring symptoms was less than 30%, according to Y-Bocs. Stereotactic electrodes were placed on the inferior thalamic peduncle. With the neurostimulator (DBS), ideal parameters were established, avoiding uncomfortable effects, with subjective reduction of OCD symptoms. After implantation, all patients were kept out of stimulation for one month during a period of surgical recovery. Then the stimulators were switched on for one year. Parameters were fixed at 5.0 V, 130 Hz and 450 microseconds. Outcomes were measured by the Y-Bocs scale, GAF scale and a neuropsychological evaluation, every three months in the stimulation period. Significant changes were observed in the Y-Bocs scores of the Friedman test. Improvement in GAF scores correlated with improvement in family and social relationships (confinement was discontinued and 60% of patients returned to work). The Y-Bocs score decreased from severe to mild symptoms (P=0.001). The GAF score increased from 20% to 70% (P=0.0001). This represents a shift from almost total family and social dependence to almost normal independence in daily life activities. Initially, patients had severe impairments in communication and social relationships, including those at work or school. For 12 months, this condition improved from moderate to mild disturbance in social relations[19]**(B)**.

Patients aged 18-65 years old who were diagnosed as having primary OCD according to DSM-IV may need DBS treatment. Only patients with a score of at least 28 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), measured twice for at least two weeks apart, should be included. Patients must have at least five years of OCD, experience significant functional impairment according to DSM-IV criterion C and a global assessment of functioning of ≤45. Treatment refractoriness was defined as any response or insufficient response following at least two treatments with a selective serotonin-reuptake inhibitor at the maximum dosage for at least 12 weeks plus one treatment with clomipramine hydrochloride for at least 12 weeks, and at least one treatment with an atypical antipsychotic for eight weeks in combination with a selective serotonin reuptake inhibitor and at least one treatment with CBT for a minimum of 16 sessions. After electrode implantation, patients entered an open phase of eight months, during which they were evaluated every two weeks for the severity of the symptoms and the optimal stimulation parameters. Once the initial and substantial decrease (an average of 6 points) in the Y-Bocs score had been obtained, usually after eight weeks of stimulation, a standardized CBT program was added (individual weekly sessions of 60 minutes for 24 weeks). After this phase, patients entered a double-blind, placebo-controlled phase. Patients were randomly assigned to two periods of two weeks with the stimulators blinded (active stimulation) at one time, and

switched off (stimulus simulation) at another time. Patients were assessed three times (baseline, after a two-week period of active or simulated stimulation, and after a second two-week period of active reverse or placebo stimulation). Treatment with CBT was continued during the crossover period. Electrode implantation was performed using a stereotactic technique targeting the nucleus accumbens. The stimulation parameters were standardized for a frequency of 130 Hz, a pulse width of 90 microseconds and a voltage of 5.0 V. Obsessive-compulsive symptoms were measured using the Y-Bocs, with scores ranging from 0 to 40; higher scores indicate more severe symptoms. Patients were defined as responders if they had a score reduction of at least 35% (Y-Bocs). Depression was classified using the Hamilton Rating Scale for Depression with 17-items (HAM-D) and anxiety was assessed using the Hamilton Anxiety Rating Scale (Hama). The Sheehan Disability scale was used to assess general symptomatic and functional deterioration, and consists of three separate classifications that assess the effect of symptoms at work, social life and family life. Open-phase stimulation resulted in a decrease in the mean Y-Bocs score of 15.7±10.8 points (46%) (P=0.001). The analysis revealed that 60% of patients had a 35% Y-Bocs score decrease, with a mean increase of 23.7±7.0 points (72%) compared with a mean decrease of 5.4±3.1 points (24%) in the group of non-responders. In the open phase, 30% of the patients reached a final Y-Bocs score below 10 (mean reduction of 81%), 20% of patients with final Y-Bocs scores between 10 and 20 (mean reduction of 51%), 20% of patients achieved a final Y-Bocs score between 20 and 30 (mean reduction of 22%) and 30% of patients achieved a final Y-Bocs score of over 30 (mean reduction of 10%). No patient worsened under stimulation. Patients with obsessive-compulsive symptoms, such as perfectionism, need for symmetry and quest for tranquillity, had an average decrease of 10% on the Y-Bocs. A significant reduction was observed in all outcome measures. In the double-blind phase, the mean Y-Bocs score difference between active and "simulated" stimulation throughout the sample was 8.8±9.1 points (P=0.003). The mean difference in Hama score between active and "simulated" stimulation was 12.1±9.1 (P=0.01), and the mean difference in Hama score between active and placebo stimulation was 11.3±7.2 (P=0.01). The improvement observed in the open phase was maintained over 12 months, in which all measures of results showed a statistically significant mean reduction between post-stimulation and baseline preoperative values. The most prominent adverse transient event related to stimulation was elevated mood or hypomania. Elevated mood was reported frequently in reactivation of stimulation after a period of no stimulation. Other adverse events were altered libido and mild forgetfulness[20](B).

All subjects were adults meeting the DSM-IV criteria for OCD, with a minimum score of 28 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs). They should have a history of five years of symptoms, refractory to treatment of OCD, with functional impact on the patient. In the 30-day postoperative period, patients were randomized to active DBS stimulation, targeting the ventral capsule/ventral striatum, or placebo stimulation. The result was measured by the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), the response being defined as a percentage change, to 35% and an effective score of ≤16 in the evaluation. It was found that there were significant reductions in the Y-Bocs score over time (p=0.0392), with a decrease of 15.67±11.60 after 12 months of activation. The categorical response and number of patients who achieved a Y-Bocs score ≤16 for the 12 months of DBS activation was 67% of patients met the criteria for response (Y-Bocs change ≥35% baseline and Y-Bocs ≤16). Within two months with configuration changes, the Y-Bocs score decreased by 33% (in ten months) and this improvement was sustained. Based on the Hamilton Depression Scale, scores significantly decreased for the whole group (p=0.0249), during the 12-month DBS. SF-36-V (vitality) increased significantly (p=0.0079). There were no serious adverse events, such as seizures or cerebral haemorrhages. All adverse events associated with implantation/anaesthesia were anticipated and limited in time. These were discomfort in the surgical site, pain in the incision, tingling, headache, nausea or numbness and sore throat. Adverse effects of stimulation, unwanted or unusual emotional effects, perceptual or somatic experiences. All these effects occur within seconds or minutes of DBS and can be reversed, usually within seconds, and always within minutes, by altering the stimulation parameters. Transient emotional effects, including euphoria, dizziness, anxiety, panic attacks or sadness may also occur. A contralateral smile accompanied by joy can be induced intraoperatively. Hypomania was observed at some point during chronic DBS. None of the participants gave a history of bipolar disorder. Difficulty

falling asleep was a common complaint that was addressed by adding required hypnotic sedatives or by adjusting the device. The clinical effects and effects of the time course of DBS discontinuation were similar, with worsening of mood or increased anxiety, signs of depression such as decreased energy or interest, and also emerged within days of device discontinuation, exacerbation of symptoms of OCD, but no intention of suicide expressed. In all cases, DBS recovery led to the reversal of transient clinical deterioration. The results indicate that the clinical efficacy of DBS in adolescents was achieved without significant neuropsychological morbidity. At 6 months post-DBS, only 2.1% of the patients showed a decline among the responders, while only 7.1% showed a decline in non-responders. In one year, 5.4% of respondents showed a decline, found in 10.7% of non-responders[21](B).

Patients (n: 10) aged 21-65 years, chronic, severe, treatment-resistant OCD (diagnosis by DSM-IV) underwent DBS. Patients score ≥25 on the Yale-Brown Obsessive Compulsive Scale (Y-Bocs), more than five years of disease, and are resistant to treatment, defined as less than 35% improvement in Y-Bocs after four different treatment regimens: (1) the use of a serotonin reuptake inhibitor (SSRI) at a sufficient dosage over a period of at least ten weeks, (2) the use of another SSRI or clomipramine hydrochloride (300 mg/d) for at least ten weeks, (3) association with lithium, buspirone hydrochloride or an antipsychotic for 10 weeks, and (4) complete cognitive-behavioural psychotherapy for a minimum of 20 sessions with documented inefficiencies. All patients underwent psychiatric examination at the beginning (preoperative), in the first week and 3, 6, 9 and 12 months after the implant. The primary outcome was the reduction of symptoms according to Y-Bocs. The following instruments were used to measure secondary outcomes: the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale (HDRS), the State-Trait Anxiety Inventory (STAI), the Hamilton Anxiety Rating Scale (Hars), Symptom Checklist 90 (SCL-90-R), Global Assessment of Functioning (GAF) and Modular System for Quality of Life (MSQL). Cognitive function was assessed by Verbal Fluency Exam (VFE). Executive performance was measured with Tower of London (TOL) test. Sustained and selective attention was measured with the Continuous Performance Test (CPT). Under local or general anaesthesia, the quadripolar electrodes were implanted stereotactically in the nucleus accumbens. The stimulation procedure was divided into three phases. In the operating room, the test stimulus was initiated, and patients were asked to report changes in mood, anxiety, alertness or body sensations. The double-blind phase began after the neurostimulator was implanted. During this time, the stimulator was turned on or off during the first three months. The patient was then migrated to the condition of another stimulus for the next three months. During stimulation, the parameters were set at 145 Hz, 90 μS and 4.5 V. After six months, stimulation was continuous in all patients, without blinding, with the option of changing the parameters every three months. In the stimulation test, anxiety, agitation, drowsiness, smell of bitter almonds and a sense of comfort were reported. All these events disappeared by changing parameters, with the exception of a patient whose anxiety lasted a few hours. Of the patients who received first stimulation and then no stimulation, 40% showed a decrease during the three months. Both deteriorated again in the following off-stimulation period. Of the patients who received no stimulation at first, then stimulation, 40% remained stable in their baseline Y-Bocs score up to the end of the three-month "off period". Patients showed substantial improvement over the six-month follow-up. Overall, mean total Y-Bocs scores of patients differed significantly between the beginning (32.2±4.0) and in the "on" stimulation period (27.9±6.4, p=0.033), but not between "off" stimulation (31.1±5.0) and "on" stimulation (27.9±6.4, p=0.205). Only 10% of the patients had a "complete response" after one year, defined as a reduction in the Y-Bocs score of more than 35%; 40% of patients achieved a "partial response", defined as a reduction of 25%-35% of the initial Y-Bocs score. The remaining patients did not improve, at least 25%, after one year. The mean Y-Bocs score decreased significantly, from 32.2 (±4.0) at baseline to 25.4 (±6.7) after 12 months (p=0.012). BDI significantly decreased from the mean 22.7 (±10.1) at baseline to 15.9 (±9.5) after 12 months (p=0.033). In addition, the mean HDRS score showed a significant decrease from 21.6 (±5.9) to 16.6 (±8.2) within one year after implantation (p=0.012). The STAI for anxiety symptoms did not improve significantly (from 56.4±13.6 to 50.7±15.3, p=0.139). The Hars score for anxiety symptoms also did not decrease significantly (from 21.2±6.7 to 15±8.5, p=0.066). The overall psychological symptom, measured by SCL-90-R, "Global Severity Index (GSI)", remained stable (from 1.3±0.7 to 1.2±0.8 at 12 months, p=0.575). In contrast, global functioning (GAF) improved significantly from 36.6 (±3.0) to 53.1 (±9.3) (p=0.012), and quality of life (MSQL) improved significantly from 41.3 (±15.8) to 53.2 (±19.8) (p=0.038). No adverse events occurred during the sur-

gical procedure. After implantation of the neurostimulator, one patient reported dysesthesia in the subclavian region, which lasted several weeks. Four patients experienced transient agitation and anxiety for several days after an increase in voltage. These effects were reversed after the reduced voltage. Two of the patients developed a hypomanic state that lasted several days and reverted spontaneously. Another patient reported difficulty concentrating and failing memory, but these side effects disappeared after the pacing parameters were altered. One patient developed suicidal thoughts after six months, being hospitalized. One patient reported an increase in the frequency of headache during the year after the implant. Another reported a shorter sleep duration and a slight increase in internal tension[22](B).

Several evaluations of obsessive-compulsive disorder patients treated with DBS have been identified. For the stimulation of the area of the nucleus accumbens/caudate nucleus, the adjacent inner capsule and the subthalamic nucleus, good effects were obtained, despite the divergent positioning of the electrodes. In all the research groups, at least 50% of the patients exhibited previously refractory improvements within one year in terms of partial response (≥25% improvement in the Yale-Brown Obsessive Compulsive Scale [Y-Bocs]). Long-term observation has shown improvements in both the degree of symptom reduction and the proportion of patients with obsessive-compulsive disorder who benefit from stimulation[3](B).

Patients (n: 6) with severe OCD were submitted to electrode implantation in the anterior limb of the internal capsule (AL/IC). After 21 months, 50% of the cases had changes in the regional activity, measured by functional magnetic resonance imaging (fMRI) and tomography by emission of tomography (PET). Another group of patients (n: 3) with severe OCD was treated with DBS for the anterior limbs of the internal capsules, with a 65% response and little adverse effect. Patients (n: 4) resistant to the treatment of OCD with severe anxiety disorder received DBS for the nucleus accumbens, with 75% of total remissions over 24 to 30 months. Patients with chronic intractable OCD were treated with DBS and electrodes placed bilaterally in the anterior limbs of the anterior capsules, with improvement in 50% of the cases. Treatment resistant severe OCD (n: 10) was treated with implanted electrodes extending into the ventral capsule and ventral commissure. The patients were followed up for 36 months. Of the patients, 40% had an improvement over 34% based on the Yale-Brown Obsessive Compulsive Scale; 20% had reductions between 25% and 35%. There was incidental improvement of depression. Side effects included asymptomatic haemorrhage, convulsion, superficial infection, worsening of symptoms when DBS stopped due to battery failure and transient hypomanic symptoms. Patient with depression and patient with obsessive-compulsive disorder had the stereotactic implant of electrodes in the thalamic inferior peduncle. Using the GAF scale, both cases showed improvement. In a multicentre study of severe OCD (n: 16) with subthalamic DBS, there was significant improvement in OCD with active stimulation, but there were 15 severe adverse events (including a cerebral haemorrhage) and 23 minor adverse events. Of the patients, 25% were recovered, using a Y-Bocs of 6 or less as an indicator of recovery. It was noted that there was no improvement in depression, and hypomania was one of the adverse events[23](B).

DISCUSSION

Due to the number of cases studied, despite the significant differences obtained with the various outcomes and measurement instruments, the results of the studies assessing DBS in the treatment of depression or OCD lack power (type II error). However, the published effects of treatment of refractory psychiatric conditions with DBS should be considered since, in the majority of cases, there has been a clear improvement in the psychiatric status of these severely ill and previously intractable patients. The various case series have been replaced by an increasing number of randomized, double-blind, phase II clinical trials comparing patients with and without use of DBS. Similarly, the adverse effects of DBS use in such patients are reduced, often reversible, spontaneously, by adjustment of treatment parameters, or are well tolerated by patients.

At present, deep brain stimulation seems to provide new options for the treatment of refractory psychiatric illnesses, including depression and OCD, but in decision making there must be rigor in the selection of refractory patients, especially in relation to severity and lack of options and the potential benefits faced with the risks involved in the procedure should be considered.

It should also be taken into account, within the injury psychosurgery, as form of treatment of refractory severe patients, as depression and obsessive-com-

pulsive disorder (OCD), ethical issues arising from the increased application of deep brain stimulation (DBS). As efforts have been made in clinical research and medical care, evaluating the role of DBS in the treatment of these patients, ethical norms should accompany this process (especially in the care setting), issues of explanation and informed consent to patient, study designs used and the explicit definition of which level of severity should be included in this therapeutic modality.

RECOMMENDATION:

Benefit

Patients with depression or OCD refractory to all appropriate forms of treatment today are candidates for treatment with deep brain stimulation.

Harm

There is an increase in the occurrence of adverse effects, mainly related to the intervention or the stimulation, being usually reversible with the change in the parameters used.

ANNEX I

Clinical question

Can patients with depression or obsessive-compulsive disorder benefit from deep brain stimulation?

Structured question

P	Patients with depression or obsessive-compulsive disorder
I	Deep brain stimulation
C	Simulation of deep brain stimulation (simulated), clinical treatment or after deep brain stimulation
O	Non-intermediary clinical outcomes

P (Patient); **I** (Intervention or Exposure); **C** (Comparison); **O** (Outcome)

Evidence search strategy

PubMed-Medline

#1: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND Random* = **426** recovered

#2: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND Prognosis/narrow[filter] = **63** recovered

#3: (((Electric Stimulation Therapy OR Deep Brain Stimulation OR DBS) AND (Temporal Lobe OR Hippocampus OR Thalamus OR Nucleus Accumbens OR Globus Pallidus OR Anterior Thalamic Nuclei OR Subthalamic Nucleus OR Corpus Callosum OR Prefrontal Cortex OR Cerebral Cortex OR Posterior Thalamic Nuclei OR Depressive Disorder, Major OR Depressive Disorder OR Depressive Disorder, Treatment-Resistant OR Obsessive-Compulsive Disorder OR Bipolar Disorder OR Depression NOT (Parkinson* OR Parkinson's disease OR dystonia OR pain))) AND (Therapy/broad[filter] OR Epidemiologic methods) = **1,877** recovered

1st RECOVERY: #1 OR #2 OR #3 = 1,893 recovered

Embase

electric AND ('stimulation'/exp/mj OR stimulation) AND ('therapy'/exp/mj OR therapy) OR deep AND ('brain'/exp/mj OR brain) AND ('stimulation'/exp/mj OR stimulation) OR DBS AND (temporal AND lobe OR 'hippocampus'/exp/mj OR hippocampus OR 'thalamus'/exp/mj OR thalamus OR nucleus AND accumbens OR globus AND pallidus OR anterior AND thalamic AND nuclei OR subthalamic AND nucleus OR corpus AND callosum OR prefrontal AND cortex OR cerebral AND cortex OR posterior AND thalamic AND nuclei OR depressive AND disorder, AND major OR depressive AND ('disorder'/exp/mj OR disorder) OR depressive AND disorder, AND 'treatment resistant' OR 'obsessive compulsive' AND ('disorder'/exp/mj OR disorder) OR bipolar AND ('disorder'/exp/mj OR disorder) OR 'depression'/exp/mj OR depression) AND [randomized controlled trial]/lim AND [embase]/lim

2nd RECOVERY = **53** recovered

Cochrane

#1 – 'deep brain stimulation

#2 – (Depressive Disorder OR Obsessive Compulsive Disorder)

3rd RECOVERY = #1 AND #2 = **25** recovered

Papers recovered

Obtaining the evidence to be used to analyse the clinical question followed the steps of: elaboration of the clinical question, structuring the question, searching for the evidence, critical evaluation and selection of the evidence, exposure of the results and recommendations.

The primary databases of scientific information consulted were Medline via PubMed and Embase; and secondary, the Cochrane Library. A manual search was carried out based on references of revisions (narratives or systematic), as well as the selected papers.

Of 21 papers (11 on depression and 10 on obsessive-compulsive disorder) considered for critical evaluation, none were excluded because of full text unavailability. After evaluation of the titles and abstracts and from the inclusion and exclusion criteria, all were used to support the synthesis of the evidence.

INCLUSION AND EXCLUSION CRITERIA OF THE PAPERS

Studies within the limits of PICO were included.

All papers recovered in the primary and secondary information bases were evaluated. In the manual search, no papers were selected.

The papers included in the evaluation are from the period between 2005 and 2013.

The main reasons for exclusion were: patient does not fit the description, performance evaluation of healthcare professionals, pilot study, post-hoc analysis, intermediate outcome, subgroup evaluation, letter, case-control design, case report, comparison between application techniques and cost.

According to the study designs

Only studies with epidemiological study design (Clinical Trial [Randomized or not], Observational Cohort or Before and After Study) and systematic reviews of epidemiological studies were included.

A critical reading was made of each of the studies to look for biases that could compromise the internal validity of the studies. In the absence of serious biases that invalidated the studies, these were included in the review.

Only studies that evaluated at least one clinical or clinically relevant outcome were included. When there was more than one publication of the same study, only the one whose clinical outcome was considered relevant and had the longest follow-up was evaluated.

When subgroup analysis was performed, which increases the possibility of random associations, the power of the study was calculated to detect the difference of the results, being considered relevant if greater than 80%.

5.2 Language

Studies available in Portuguese, English or Spanish were included.

5.3 According to the publication

Only papers whose complete texts were available were considered for critical evaluation.

METHOD OF CRITICAL EVALUATION

When, after applying the inclusion and exclusion criteria, the evidence selected in the search was defined as a cross-sectional study or randomized controlled clinical trial (RCT), it was submitted to an appropriate checklist (Table 1) for critical evaluation

TABLE 1 - CRITICAL EVALUATION SCRIPT OF RANDOMIZED CONTROLLED CLINICAL TRIALS

Study data – Reference, study design, Jadad, strength of evidence	**Sample calculation** – Estimated differences, power, level of significance, total patients
Patients selection – Inclusion and exclusion criteria	**Patients** – Recruited, randomized, prognostic differences
Randomization – Blinded description and allocation	**Patients follow-up** – Time, losses, migration
Treatment Protocol – Intervention, control and blinding	**Analysis** – Treatment intention, analysed, intervention and control
Outcomes considered – Primary, secondary, measurement instrument of outcome of interest	**Result** – Benefit or harm in absolute data, benefit or harm in mean

TABLE 2 - CRITICAL EVALUATION SCRIPT OF COHORT STUDIES

Representativeness of exposed and selection of non-exposed (max 2 points)	Exposure definition (max 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (max 1 point)	Comparability on the basis of design or analysis (max 2 points)	Evaluation of the outcome (max 1 point)	Appropriate follow-up time (max 2 points)	Score and level of evidence

(Quadas[24] or Consort[25]). The controlled clinical trials were evaluated according to the Jadad[26] score and/or the Grade[27] score.

The critical evaluation of the included studies makes it possible to classify them by the Oxford scale[28] as evidence strength 1b or 2b, and corresponding degree of recommendation A or B, respectively. Systematic reviews were classified on the strength of evidence 1a or 2a, and degrees of recommendation A or B, respectively.

The selected evidence defined as a comparative study (observational cohorts or non-randomized clinical trial) was submitted to an appropriate critical evaluation checklist (Table 2), allowing the classification of the study according to the Newcastle-Ottawa Scale score[29], considering the consistent cohort studies with score ≥6 and inconsistent <6.

EXPOSURE OF RESULTS

For results with available evidence, the population, intervention, outcomes, presence or absence of benefit and/or harm and controversies will be defined in a specific way, whenever possible.

The results will be preferably exposed in absolute data, absolute risk, number needed to treat (NNT) or number needed to harm (NNH) and possibly in mean and standard deviation (Table 3).

TABLE 3 - WORKSHEET USED TO DESCRIBE AND PRESENT THE RESULTS OF EACH STUDY.

Evidence included
Study Design
Population selected
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ration, mean

RECOMMENDATIONS

The recommendations will be prepared by the authors of the review, with the initial characteristic of synthesis of the evidence, being submitted to the validation by all the authors participating in the preparation of the guideline.

The degree of recommendation to be used stems directly from the available strength of the studies included according to Oxford[28] and the use of the Grade[27] system.

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