Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson’s disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial

Eugénie Lhommée, Lars Wojtecki, Virginie Czernecki, Karsten Witt, Franziska Maier, Lisa Tonder, Lars Timmermann, Thomas D Hälbig, Fanny Pineau, Franck Durif, Tatiana Witjas, Marcus Pinsker, Maximilian Mehndon, Friederike Sixel-Daring, Andreas Kupsch, Rejko Kruger, Saskia Elben, Stephan Chabardes, Stéphane Thobois, Christine Breffel-Courbon, Fabienne Ory-Magne, Jean-Marie Regis, David Maltête, Anne Sauvaget, Jorn Rau, Alfons Schnitzler, Michael Schipbach, Carmen Schade-Brittinger, GuntherDeuschl, Jean-Luc Houeto, Paul Krack, in collaboration with the EARLYSTIM study group

Summary

Background Although subthalamic stimulation is a recognised treatment for motor complications in Parkinson’s disease, reports on behavioural outcomes are controversial, which represents a major challenge when counselling candidates for subthalamic stimulation. We aimed to assess changes in behaviour in patients with Parkinson’s disease receiving combined treatment with subthalamic stimulation and medical therapy over a 2-year follow-up period as compared with the behavioural evolution under medical therapy alone.

Methods We did a parallel, open-label study (EARLYSTIM) at 17 surgical centres in France (n=8) and Germany (n=9). We recruited patients with Parkinson’s disease who were disabled by early motor complications. Participants were randomly allocated (1:1) to either medical therapy alone or bilateral subthalamic stimulation plus medical therapy. The primary outcome was mean change in quality of life from baseline to 2 years. A secondary analysis was also done to assess behavioural outcomes. We used the Ardouin Scale of Behavior in Parkinson’s Disease to assess changes in behaviour between baseline and 2-year follow-up. Apathy was also measured using the Starkstein Apathy Scale, and depression was assessed with the Beck Depression Inventory. The secondary analysis was done in all patients recruited. We used a generalised estimating equations (GEE) regression model for individual items and mixed model regression for subscores of the Ardouin scale and the apathy and depression scales. This trial is registered with ClinicalTrials.gov, number NCT00354133. The primary analysis has been reported elsewhere; this report presents the secondary analysis only.

Findings Between July, 2006, and November, 2009, 251 participants were recruited, of whom 127 were allocated medical therapy alone and 124 were allocated bilateral subthalamic stimulation plus medical therapy. At 2-year follow-up, the levodopa-equivalent dose was reduced by 39% (−363·3 mg/day [SE 41·8]) in individuals allocated bilateral subthalamic stimulation plus medical therapy and was increased by 21% (245·8 mg/day [40·4]) in those assigned medical therapy alone (p=0.0001). Neuropsychiatric fluctuations decreased with bilateral subthalamic stimulation plus medical therapy during 2-year follow-up (mean change −0·65 points [SE 0·15] and did not change with medical therapy alone (−0·02 points [0·15]); the between-group difference in change from baseline was significant (p=0·0028). At 2 years, the Ardouin scale subscore for hypodopaminergic behavioural disorders decreased with bilateral subthalamic stimulation plus medical therapy (mean change −1·26 points [SE 0·35]) and had increased with medical therapy alone (1·12 points [0·35]); the between-group difference was significant (p<0·0001). Mean change from baseline at 2 years in the Ardouin scale subscore for hypodopaminergic behavioural disorders, the Starkstein Apathy Scale score, and the Beck Depression Inventory score did not differ between treatment groups. Antidepressants were stopped in 12 patients assigned bilateral subthalamic stimulation plus medical therapy versus four patients allocated medical therapy alone. Neuroleptics were started in nine patients assigned medical therapy alone versus one patient allocated bilateral subthalamic stimulation plus medical therapy. During the 2-year follow-up, two individuals assigned bilateral subthalamic stimulation plus medical therapy and one patient allocated medical therapy alone died by suicide.

Interpretation In a large cohort with Parkinson’s disease and early motor complications, better overall behavioural outcomes were noted with bilateral subthalamic stimulation plus medical therapy compared with medical therapy alone. The presence of hypodopaminergic behaviours and neuropsychiatric fluctuations can be judged additional arguments in favour of subthalamic stimulation if surgery is considered for disabling motor complications.

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Research in context

Evidence before the study

We searched PubMed for original research and review articles published in English, French, or German before October, 2017, with the keywords “Parkinson’s disease” combined with “deep brain stimulation” or “subthalamic nucleus” and “behavior” or “mood” or “impulse control disorder,” or “addiction.” The scientific literature is highly contradictory, particularly with respect to hyperdopaminergic behaviours classified as impulse control disorders or behavioural addictions. Hyperdopaminergic behavioural disorders are either reported to worsen or new disorders arise, or to strikingly improve on subthalamic stimulation, and most studies do not include comprehensive assessment of behaviour. The most frequent hyperdopaminergic behaviours reported are depression and apathy. Most randomised controlled trials do not include specific assessment of apathy, find no difference in the frequency of depression, and report anxiety to be either unchanged or improved. Many papers report apathy as a complication and the discussion is controversial concerning its causes, some authors suggesting apathy might be linked directly to subthalamic stimulation, others reporting apathy as being unmasked by reduction of dopaminergic treatment. The last view is supported by the findings of one randomised controlled trial reporting improvement in postoperative apathy after re-introduction of dopamine agonists. Only one non-controlled study addressed neuropsychiatric non-motor fluctuations and reported improvement. No randomised controlled trial has addressed this issue.

Added value of this study

To our knowledge, our study is the first large multicentre randomised trial to compare the effects of subthalamic stimulation and best medical treatment on the whole range of mood and behavioural disorders recorded in patients with Parkinson’s disease, over a 2-year period. We used the Ardouin scale to assess behaviour outcomes, which is a validated semi-structured interview dedicated to Parkinson’s disease that assesses hypodopaminergia (including apathy and depression), neuropsychiatric non-motor fluctuations (eg, ON state euphoria and OFF state dysphoria), and hyperdopaminergia (such as risk-taking behaviours and night-time hyperactivity). The strength of the Ardouin scale is that it is based on an exhaustive clinic interview led by a psychiatrist or a psychologist with experience in the management of patients with Parkinson’s disease. This scale, which has been validated against gold-standard psychiatric tools, has clear rating guidelines and accounts for changes in the patient’s habits and mood and the impact on their personal and social life. Subthalamic stimulation alleviated neuropsychiatric non-motor fluctuations and permitted better control of hyperdopaminergic behaviours without substantial adverse occurrence of apathy, depression, or anxiety, compared with best medical treatment.

Implications of all the available evidence

Subthalamic stimulation in patients with Parkinson’s disease and early motor fluctuations is effective at improving neuropsychiatric non-motor fluctuations and reduces behavioural side-effects of dopamine replacement therapy. Our results are clinically relevant and suggest that subthalamic stimulation, similar to other non-pulsatile treatments of Parkinson’s disease, is relatively safe and useful for management of psychobehavioural manifestations in Parkinson’s disease. This finding allows for a change in paradigm: whereas all type of behavioural disorders used to be judged contraindications for surgery, the presence of disabling hyperdopaminergic behaviours and neuropsychiatric non-motor fluctuations in patients with Parkinson’s disease who are candidates for surgery should rather be considered as arguments in favour of subthalamic nucleus stimulation.

Introduction

Many cognitive, neuropsychiatric, and behavioural modifications have been described in both patients with Parkinson’s disease 1 who have received no treatment and those who have been treated with medical and surgical 2 therapies. Dopamine replacement therapy and subthalamic deep-brain stimulation are established treatments for motor complications of Parkinson’s disease.3 Controversial results reporting behavioural side-effects of these therapies leave the neurologist uncertain as to how to best manage medications and stimulation variables postoperatively.4 On the one hand, after subthalamic stimulation, neurologists must frequently manage the underdiagnosed hypodopaminergic state (eg, apathy, depression, anxiety).5 This state, which is probably linked to mesolimbic dopaminergic deficits, can be unmasked by a substantial decrease in dopaminergic medications after subthalamic stimulation.6 On the other hand, the neurologist has to manage many diverse and potentially devastating hyperdopaminergic states7 that are linked to dopamine replacement therapy. These states range from simple excessive motivation and drive in various activities to potentially devastating behavioural addictions, impulse control disorders, punding, and addiction to dopaminergic treatment.8

A hyperdopaminergic state has been reported to improve,9–11 remain unchanged, or begin after subthalamic surgery.12 Moreover, most patients with motor fluctuations also have neuropsychiatric fluctuations.13 Up to now, no randomised controlled trials of subthalamic stimulation in Parkinson’s disease have assessed these mood swings. This research area is important, because mood and behaviour have a greater effect on quality of life in Parkinson’s disease than do motor complications.14 and behavioural disorders are over-represented in Parkinson’s disease candidates for surgery.9 Thus, the
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