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PAPER

Chronic deep brain stimulation for the treatment of tremor in multiple sclerosis: review and case reports

H A Wishart, D W Roberts, R M Roth, B C McDonald, D J Coffey, A C Mamourian, C Hartley, L A Flashman, C E Fadul, A J Saykin

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See end of article for authors' affiliations

Correspondence to: Dr H A Wishart, Department of Psychiatry, Dartmouth Medical School, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03756-0001, USA; heather.wishart@dartmouth.edu

Background: Deep brain stimulation (DBS) offers a non-ablative alternative to thalamotomy for the surgical treatment of medically refractory tremor in multiple sclerosis. However, relatively few outcomes have been reported.
Objective: To provide a systematic review of the published cases of DBS use in multiple sclerosis and to present four additional patients.
Methods: Quantitative and qualitative review of the published reports and description of a case series from one centre.
Results: In the majority of reported cases (n = 75), the surgical target for DBS implantation was the ventrointeromedial nucleus of the thalamus. Tremor reduction and improvement in daily functioning were achieved in most patients, with 87.7% experiencing at least some sustained improvement in tremor control postsurgery. Effects on daily functioning were less consistently assessed across studies; in papers reporting relevant data, 76.0% of patients experienced improvement in daily functioning. Adverse effects were similar to those reported for DBS in other patient populations.
Conclusions: Few of the studies reviewed used highly standardised quantitative outcome measures, and follow up periods were generally one year or less. Nonetheless, the data suggest that chronic DBS often produces improved tremor control in multiple sclerosis. Complete cessation of tremor is not necessarily achieved, there are cases in which tremor control decreases over time, and frequent reprogramming appears to be necessary.

Multiple sclerosis can be associated with tremor in the arms, legs, trunk, and head, although the upper extremities are most commonly affected.[1 2] In a recent study of 100 outpatients with definite multiple sclerosis, action tremor was detected on neurological examination in 58 cases, while in contrast to some previous reports, rest and rubral tremors were not observed.[1] The action tremor of multiple sclerosis can have postural or kinetic components (including intention), and may affect the more proximal or more distal forearm.[1–3] In general, tremor associated with multiple sclerosis is thought to be related to dysfunction of the cerebellum or its connections, though further research is needed to explore its pathophysiology fully.[1]

Medical treatment of tremor in multiple sclerosis is often less than satisfactory[1 2] and ablative thalamotomy, while effective in selected patients,[4] may not produce sustained benefit.[5 6] Chronic deep brain stimulation (DBS) through implanted electrodes provides an alternative. Given the success of DBS in the treatment of Parkinson's disease and essential tremor, this procedure has also been used in multiple sclerosis. In this paper we present a review of the published reports on this subject, as well as a case series of individuals who received bilateral implantation at our centre.

METHODS

Papers for the literature review were located using relevant keywords (deep brain stimulation, neurostimulation, thalamic stimulation, multiple sclerosis) and associated search terms in Ovid Medline 1966 to 2002, and by searching the reference list of each article recovered. This strategy yielded 14 full reports of DBS in multiple sclerosis, all of which contained data relevant to the review (table 1). All studies were modest in size, ranging from one to 14 patients. Across all studies, the total number of patients who received completed DBS implantation was 75; in some cases, additional patients were initially studied, but DBS implantation was not completed for various reasons (see Results). In some studies, the patients with multiple sclerosis were part of a larger sample composed mainly of individuals with Parkinson's disease or essential tremor. Follow up periods ranged from less than three months to more than 12 months, with most studies (n = 7) in the 6 to 12 month range. Each study was reviewed for selection criteria, surgical target, and primary outcome variables, including tremor suppression, improvement in daily functioning, and adverse effects.

For the purpose of this review, tremor suppression was defined according to the percentage of patients showing sustained improvement (to the end of the study period), to any degree and on any type of tremor scale or tremor measurement device. Improvement in daily functioning was defined according to the percentage of patients showing sustained improvement in functions such as feeding, holding and manipulating household objects, and quality of life. For the most part, reports of improvement in daily functioning were based on patient self report, while improvement in tremor control was based on paper and pencil testing, tremor amplitude scales, or tremor measurement devices. Also included in this report are original data from the complete consecutive series (n = 4) of multiple sclerosis patients who have received DBS implantation at our hospital.

RESULTS

Review of previously published data

Inclusion criteria and sample characteristics

Six studies reported explicit criteria for selecting patients for DBS surgery (Montgomery *et al*,[3] Hooper *et al*,[17] Benabid *et al*,[10]

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Table 1 Studies describing chronic deep brain stimulation in multiple sclerosis

Study [ref]	n*	Inclusion criteria/ sample characteristics	Locus	Follow up	Adverse effects	Tremor suppression†	Effect on daily functions‡
Brice and McLellan, 1980[7]	2	Severe disabling tremor; sensation, power, finger movements relatively well preserved; clinically stable for 6 months; failure to respond to drug treatment	Bilateral subthalamic	5–6 months	Not reported separately	100%	100%
Nguyen and Degos, 1993[8]	1	Severe tremor	Unilateral VIM	17 months	None reported	100%	100%
Seigfried and Lippitz, 1994[9]§	9	Not reported	Unilateral VIM	Not reported	None	78%	Not reported
Benabid *et al*, 1996[10]	4	Severe tremor; failure to respond to drug treatment	VIM	3 to ⩾6 months	Microhaematoma (1 MS patient); no other persistent effects; transitory effects not separately reported for MS subsample	50%	Not reported separately
Geny *et al*, 1996[11]¶	13	Disabling tremor; no relapse within preceding 6 months	Unilateral VIM	3 months	Transitory paresis in lower limb (1 case); dysaesthesiae of <1 min at onset of stimulation (all cases); asthenia (1 case)	69%	92%
Whittle *et al*, 1998[12]	5	Disabling UE movement disorder; absence of predominantly postural axial tremor or severe neurological dysfunction; ability to locate an effective surgical target	Ventrolateral thalamus	Not reported	Mood disturbances in some	Benefit in some or all patients; no detailed report	Not reported
Hay, 1999[13]	1	Not specifically reported (single case study)	Unilateral thalamus	2 months	None reported	100%	Not reported
Montgomery *et al*, 1999[3]	14	Disabling UE tremor without other weakness, sensory, or other problems that would continue to limit functioning; clinically stable for 6 months; no significant speech or swallowing problems; no severe cognitive disability	VIM	<3–12+ months	Intracerebral haematoma (1 case); transient paraesthesiae when stimulator turned on (most cases)	100%	Not reported
Schulder *et al*, 1999[2]	5	Disabling UE tremor; failure to respond to drug treatment	Unilateral VIM	⩾6 months	None	100%	60%
Taha *et al*, 1999[14]**	2	Bilateral limb tremor, head tremor, or voice tremor	VIM	~10 months	Not reported separately for MS patients; no haemorrhage or infarction	100%	Not reported
Schuurman *et al*, 2000[15]	5	Severe UE tremor present at least one year despite drug treatment; age 18 or older; no significant cognitive dysfunction; no contraindications to surgery; no advanced cerebral atrophy; no previous thalamotomy	Unilateral or Bilateral VIM	6 months	Dysarthria, gait/balance disturbance, arm ataxia (3 patients); intracerebral haemorrhage (1 case of entire larger sample)	General improvement, not individually reported	No significant overall improvement; not individually reported
Matsumoto *et al*, 2001[16]	3	Severe UE tremor; clinically definite MS; no significant weakness or sensory loss in the hands; absence of arrhythmic movement disorder; clinically stable for preceding 3 months; no dementia	Unilateral VIM	12 months	None	100%	0%
Hooper *et al*, 2002[17 5]††	10	Disabling UE tremor for at least 12 months that had not responded to drug treatment; established diagnosis of MS; no major relapse for 6 months; no severe sensory or motor impairment that would continue to limit functioning; capacity to give informed consent	Unilateral thalamus	12 months	Upper limb paraesthesiae when the DBS was turned on; transitory limb weakness (2 cases), infection at site of IPG necessitating its removal (1 case); intraoperative hypoxic episode (1 case); small thalamocapsular haemorrhages at site of DBS implantation with persistent changes in functioning (2 cases); seizures (2 cases, 1 seizure each)	100%	68 to 78% were same or better at 12 months on two scales; other measures showed no effect

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Table 1 Continued

Study [ref]	n*	Inclusion criteria/ sample characteristics	Locus	Follow up	Adverse effects	Tremor suppression†	Effect on daily functions‡
Nandi *et al*, 2002[18]	1	Severe, disabling, progressively worsening UE tremor; gait dysfunction with leg ataxia (single case study)	Unilateral zona incerta	12 months	Worsening of walking and left foot dystonia developed between approximately months 9 and 12	100%	100%

*Number of patients with multiple sclerosis in whom implantation of a chronic stimulator was completed.
†As measured by the percentage of patients showing any sustained improvement (to the end of the follow up period in study) to any degree on any type of tremor scale or instrumentation.
‡As measured by the percentage of patients showing sustained improvement in daily functions such as feeding, holding and manipulating household objects, or subjective quality of life in everyday contexts.
§One patient with multiple sclerosis had bilateral stimulators; data available are for unilateral stimulation (first side).
¶Additional clinical follow up data available. Tremor suppression data are for proximal upper extremity tremor; additional less consistent improvement occurred in distal upper extremity and some improvement occurred in those with lower extremity tremor.
**Mean follow up period was 10 months for the entire sample, including six patients with Parkinson's disease, 15 with essential tremor, and two with multiple sclerosis; the follow up period for the two patients with multiple sclerosis was not reported separately. In the entire sample, 19 patients underwent either staged or simultaneous VIM implantation, while four received thalamotomy followed by unilateral VIM implantation; it is unclear whether either of the patients with multiple sclerosis was among the minority receiving the combination of thalamotomy and DBS.
††Specific targets within the thalamus were 1 mm posterior to AC-PC midpoint and from 11–15 mm lateral to midline, adjusted in 2 mm increments to the locus where stimulation produced tremor suppression without adverse neurophysiological effects.
MS, multiple sclerosis; UE, upper extremity; VIM, ventrointeromedial nucleus of the thalamus.

Whittle *et al*,[12] Schurrman *et al*,[15] Matsumoto *et al*,[16]), while the others generally provided sample or case descriptions (table 1). Inclusion criteria or sample characteristics included severe or disabling tremor in 11 of the 14 studies. Other relatively common factors were failure to respond to medical treatment (five studies), absence of other severe sensory or motor problems that would continue to limit functioning even if tremor were alleviated (five studies), clinically stable disease for three to six months before surgery (five studies), and relatively preserved cognitive function (four studies). Additional specific factors are listed in table 1. Other investigators may have used these or other inclusion/exclusion criteria, but did not describe them in their reports. Most studies did not specify the numbers of patients who were considered but rejected for surgery, possibly because selection had begun earlier in the referral process, before the study authors had contact with the patients. An exception is the study by Whittle *et al*,[12] in which it was reported that 12 of 17 patients referred for surgery did not complete the procedure because they did not meet inclusion criteria (table 1). Another is the study by Matsumoto *et al*,[16] in which seven of 16 patients referred for surgery did not have the procedure, including two who met inclusion criteria but declined the surgery, four who were denied insurance coverage, and one whose movement disorder was ultimately deemed to be ataxia. Of note, the remaining patients in the Matsumoto study received either thalamotomy (n = 6) or DBS (n = 3) but the results were reported for the most part considering both groups together.

Surgical procedures

The surgical target for DBS implantation was the ventrointeromedial nucleus of the thalamus (VIM) in the majority of studies (table 1). Alusi *et al* noted that the nucleus ventralis oralis posterior rather than the VIM has also been chosen by some as a preferred target for DBS implantation in multiple sclerosis.[4] Most groups reported detailed intraoperative stimulation and recording procedures for refining the ultimate location of implantation, based on maximising tremor suppression while minimising adverse effects. Geny and colleagues observed that the effective VIM site in multiple sclerosis is often dorsal and lateral to the VIM site that is effective in Parkinson's disease, and that the exact location of the stimulator within the VIM must be selected with attention to the somatotopic distribution within the nucleus.[11] Nguyen and Degos found that stimulation of the upper VIM region was most effective in controlling proximal tremor, while stimulation of the lower part of the VIM was most effective in controlling distal tremor.[8] In most cases, stimulator implantation was unilateral, but bilateral implantations (either staged or simultaneous) and implantations contralateral to a previous thalamotomy were also reported. In a small number of studies, chronic implantation of DBS was intended but not completed at the time of surgery. Reasons for failure to proceed to implantation included complications during surgery (one of 15 cases in the Montgomery series[3]); failure to locate an effective target (three of eight patients who otherwise met inclusion criteria in the Whittle series[12]; three of 15 cases in the Hooper series[5]); and a positive benefit of microelectrode insertion alone (two of 15 cases in the Hooper series[17]).

Tremor suppression and daily functioning

Tremor reduction and improvement in daily functioning were achieved in the majority of cases (table 1). Twelve of the 14 studies reported sufficient data to determine the percentage of patients experiencing improved tremor control. Those 12 studies involved a total of 65 patients, of whom 57 (88%) experienced sustained improvement in tremor control post-surgery. Effects on daily functioning were less consistently assessed across studies, with only six studies reporting sufficient data to determine effects in this domain. These six studies involved 25 patients, of whom 19 (76%) experienced improvement in daily functioning. Although data on frequency of reprogramming were not generally reported in detail in these studies, it appeared that reprogramming was required relatively often to maintain optimal tremor control while minimising undesired side effects.

Adverse effects

Across all 14 studies, intracerebral haemorrhage occurred in four or possibly five patients.[3 10 15 17] One was a microhaematoma, the effects of which resolved within three months.[10] In the case of Montgomery *et al*,[3] the haematoma was attributable to the surgery rather than to the stimulator (which was never placed), and the patient also experienced tremor reduction and transient dysarthria. Two cases involved small thalamocapsular haemorrhages at the site of DBS implantation which led to persistent changes in functioning.[17] In another study, which included patients with various tremor aetiologies, there was relatively little

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detail about the haemorrhage and it was unclear whether or not it was a patient with multiple sclerosis who was affected.[15]

In the entire sample of 75 patients in whom DBS implantation was completed, one developed a recurrent infection at the site of the internal pulse generator, which necessitated removal of the unit[17]; and two had seizures, one at one week postsurgery and the other at eight weeks.[17] Paraesthesiae at the onset of stimulation were relatively common across studies, but tended to be brief and mild. Other adverse effects were generally mild and in some cases transitory, and included dysarthria, disequilibrium, and limb weakness.

Six studies reported data on the presence or absence of exacerbations of multiple sclerosis after surgery (table 2). These studies involved 38 patients, of whom six or seven (16–18%) had an exacerbation within the follow up period. Only three of those exacerbations occurred within a month of surgery. Given variable presurgical baselines and postoperative follow up periods across studies, it was unclear whether this represented a significant change from the patients' baseline status. Only three studies (involving 18 patients) reported sufficient data to allow calculation of annualised per patient exacerbation rates before and after surgery.[7 11 16] All three of these studies gave a baseline exacerbation rate of zero (because recent exacerbation was an exclusion factor for surgery). Postoperatively, the annualised exacerbation rate was 0.17 per patient in these three studies.

Dartmouth-Hitchcock case series

Table 3 presents the data for the small consecutive series of patients with multiple sclerosis who have received DBS surgery for treatment of drug refractory tremor at our medical centre. This sample is distinct in that all patients had bilateral stimulator implantation (either staged or simultaneous). In addition, the follow up period from initial surgery averaged approximately 22 months, somewhat longer than many of the reports published to date. The surgical target was the ventrolateral thalamus in all cases, with the ultimate placement being determined on the basis of intraoperative response. One additional patient had a seizure intraoperatively, so implantation was not completed; that patient remains a potential candidate for surgery at a future date. The four remaining patients all experienced a significant improvement in tremor control postsurgery, and in each case better tremor control translated into improvements in aspects of daily functioning. However, reprogramming was needed to maintain optimal tremor control, and even so, the degree of control was not necessarily equal for left and right extremities. In addition, tremor control on at least one side clearly declined over time in three cases, though all patients still functioned above their presurgical baselines. One patient reported the sudden onset of unpleasant

Table 2 Exacerbations of multiple sclerosis before and after surgery

Study [ref]	n	Exacerbation-free baseline (months)	Follow up period for exacerbation data (months)	Postoperative exacerbations	Comments
Brice and McLellan, 1980 [7]	2	6 months	5–6 months	0	No changes in clinical status consistent with relapse occurred
Geny *et al*, 1996 [11]	13	6 months	12 months	3	Three patients had a relapse of their MS at 4, 6, and 12 months postsurgery, respectively; no change in average EDSS for the group
Montgomery *et al*, 1999 [3]	14	6 months	<3–12+ months	1	One patient had an exacerbation 3 days postsurgery, at the time of a UTI. This decreased the patient's lower extremity power and necessitated increased use of a wheelchair
Schulder *et al*, 1999 [2]	5	Not specified	⩾6 months	2	Two patients had an exacerbation within one month of surgery; both responded to high dose intravenous steroids. In one, new brain stem lesions were evident on MRI but not near the site of the electrode. No change in individuals' EDSS scores
Matsumoto *et al*, 2001 [16]	3	3 months	12 months	0	No exacerbations
Nandi *et al*, 2002 [18]	1	Not specified; had progressive worsening of tremor in the 6 months before surgery	12 months	?	The patient experienced progressive worsening of walking, and left foot dystonia developed between approximately 9 and 12 months post-surgery. It is unclear whether this represented a discrete relapse or continuation of the progression that was evident before surgery

In general, the papers did not give specific criteria for exacerbation, but did provide clinical descriptions (summarised here).
EDSS, expanded disability status scale; MS, multiple sclerosis; MRI, magnetic resonance imaging; UTI, urinary tract infection.

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Table 3 Dartmouth-Hitchcock case series

Patient	Patient description (age/sex/disease duration*)	Duration of follow up	Annualised reprogramming frequency	Final DBS settings†	Tremor rating‡	Tremor suppression: description of longitudinal findings	Adverse effects
1	50/M/10	20 months	2.9	R stimulator: 3.5/90/160/B; L stimulator: 2.5/90/130/M	LUE: 3/1; RUE: 3/1	Initial cessation of LUE tremor and significant decrease in RUE tremor. Effectiveness declined over time, though status is still improved relative to baseline with optimal programming	Transient episode of RUE weakness; transient episode of diplopia; no MS exacerbations
2	49/F/10	15 months for first implant; 3 months for second implant	5.6	R stimulator: never turned on; L stimulator: 1.5/60/90/B	LUE: 3/na; RUE: 3/0 (3/1when stimulator turned off)	Improved, most notably in the RUE; however, left stimulator was ultimately removed (see text). Initial benefit from surgery alone for right stimulator, which was never turned on. Progression of LUE tremor occurred over time; final tremor rating was unavailable as the patient did not return to clinic	Transient pain and swelling around insertion site initially; transient paraesthesiae, relieved by temporarily turning off the stimulator; no MS exacerbations
3	37/F/2	31 months for 1st implant; 30 months for 2nd implant	3.1	R stimulator: 4.8/120/145/M; L stimulator: 1.8/60/135/M	LUE: 3/1; RUE: 3/1	Improved; no significant decline in benefit with optimal programming	Dysarthria§; one exacerbation 4 weeks after second implant
4	50/F/14	21 months	3.4	R stimulator: 3.3/120/130/B; L stimulator: 3.0/120/145/B	LUE: 3/0; RUE: 3/0	Significant bilateral improvement initially; eventually had return of bilateral moderate to wide amplitude tremor (LUE worse than RUE), though status is still improved relative to baseline with optimal programming	No adverse effects; no MS exacerbations

Postoperative magnetic resonance imaging revealed no evidence of intraoperative haemorrhage. One additional patient had an intraoperative seizure so implantation was not completed at that time. Exacerbation was defined as the emergence of a new clinical symptom or reappearance of a previous symptom of multiple sclerosis.[20]
*Age (at time of surgery, years), sex (M, male; F, female), disease duration (years from diagnosis to surgery).
†Voltage/pulse width/frequency/monopolar (M) or bipolar (B).
‡Tremor rating (baseline/postoperative): 0, absent; 1, mild; 2, moderate; 3, severe. Postoperative ratings were made one month after surgery with stimulator turned on, unless otherwise specified.
§Reprogramming led to an acceptable balance between tremor control and dysarthria.
L, left; LUE, left upper extremity; MS, multiple sclerosis; R, right; RUE, right upper extremity.

paraesthesiae, dizziness, and nausea 15 months after an otherwise beneficial implantation. Although it was not possible to detect the source of the problem, the unit was removed at the patient's request and her complaints resolved.

DISCUSSION

Deep brain stimulation offers a non-ablative alternative to thalamotomy for the surgical treatment of drug refractory tremor. Relatively few studies of outcome with this procedure have been reported in multiple sclerosis. The studies published to date involve a total of 75 completed implantations, and this report describes four additional cases. The compiled data suggest that chronic DBS often produces sustained improvement in tremor control in multiple sclerosis, as measured by tremor scales and self report instruments, for follow up periods of several months to a year. Nevertheless, these studies also show that complete cessation of tremor is not necessarily achieved, that there are cases in which tremor control decreases over time, and that frequent reprogramming appears to be necessary. Furthermore, the only direct comparison (to our knowledge) of DBS and ablative surgery in patients with multiple sclerosis showed no clear advantage of one method over the other, though the case sample was only a relatively small subset of a larger mixed sample in that study.[15]

Although patient selection criteria were not explicitly described in all studies, the more commonly used indications for surgery appeared to be severe or disabling tremor, failure to respond to medical treatment, absence of other severe sensory or motor problems that would continue to limit functioning even if tremor were alleviated, clinically stable disease for three to six months before surgery, and relatively preserved cognitive function.

Outcomes assessment—in terms of tremor measurement and effects on daily activities—could be improved in future studies of DBS in multiple sclerosis. Matsumoto and colleagues provide a review of considerations and options for measuring tremor suppression and the practical effects of DBS surgery in multiple sclerosis.[16] They present a clinical tremor rating scale, a novel quantitative movement analysis technique, and a box-and-blocks test of prehensile function

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which appear promising. In that study, preoperative quantitative movement analysis data appeared to have value in predicting which patients would benefit most from surgery.

Whether effective tremor suppression translates to sustained improvement in daily living is somewhat difficult to assess and has received less empirical attention than tremor suppression on its own. In the studies from which relevant information could be gleaned, 76% of patients with multiple sclerosis showed benefit in terms of ability to grasp objects, self feed, print, write, or perform other everyday functions.[7 8 11 18] These studies, however, accounted for only 25 of the 75 patients reported so far, and some studies showed no significant benefit in terms of everyday functioning (for example, Matsumoto[16]). Thus the practical impact of chronic DBS on everyday activities requires further examination, giving careful attention to selection of outcome measures appropriate to the range of potential benefit in the sample being studied.[16] In some samples, regaining the ability to self feed, even at a rudimentary level, may translate to significantly improved quality of life and reduced patient care. In other samples, higher levels of independence in more complex daily functions may need to be measured as an outcome of treatment. One study reported a prevalent reduction in self reported fatigue as a function of decreased tremor during everyday activities,[11] suggesting that it would be useful to include measures of fatigue in future trials. Given reported changes in cognitive and emotional status after DBS implantation in patients with Parkinson's disease, neuropsychological and psychiatric monitoring may also prove useful in multiple sclerosis.

The ventrointeromedial nucleus of the thalamus has been the most common surgical target for multiple sclerosis tremor, the ultimate placement being determined on the basis of, among other considerations, intraoperative tremor suppression relative to adverse effects[17] and the somatotopic distribution of the intended target relative to the locus of the tremor.[3 8] As noted, reprogramming is necessary to maintain effects over time, though whether that is related to underlying disease progression, declining effectiveness of the DBS, or both, is not clear. Some early decline in tremor suppression may be related to loss of microthalamotomy effects.[17] Of note, one of the larger studies of DBS in multiple sclerosis reported no decline in response to optimally programmed stimulation during the follow up period; although stimulation levels had to be reprogrammed frequently, patients did not require progressively increased voltage, frequency, or pulse width of stimulation over time.[3] Adverse effects are similar to those reported in other patient populations undergoing DBS implantation.[19] Multiple sclerosis exacerbations have been reported after DBS implantation, but the available data do not clearly indicate whether they represent a change in exacerbation frequency relative to presurgical baseline.

Conclusions

Published reports indicate that chronic DBS is a relatively safe and effective means of reducing, but not eliminating, medically refractory tremor in multiple sclerosis. Safety considerations include risk of intracerebral haemorrhage. One limitation of most available studies is the relatively brief duration of follow up. Longer term outcome studies are needed.[2] A second limitation relates to the nature of the outcomes assessments. Multidimensional assessment appropriate to the expected range of surgical benefit is most likely to be an accurate reflection of the effects of surgery.[16] Therefore, prospective longitudinal studies using multidimensional outcome measurements are needed.

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Authors' affiliations

H A Wishart, R M Roth, B C McDonald, L A Flashman, A J Saykin, Department of Psychiatry, Dartmouth Medical School, Lebanon, New Hampshire, USA
D W Roberts, C Hartley, Department of Surgery, Dartmouth Medical School
D J Coffey, C E Fadul, Department of Medicine, Dartmouth Medical School
A C Mamourian, Department of Radiology, Dartmouth Medical School

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