OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Article

Sustained Medication Reduction Following Unilateral VIM Thalamic Stimulation for Essential Tremor

Andrew S. Resnick[1,2], Michael S. Okun[2], Teresita Malapira[2], Donald Smith[3], Fernando L. Vale[3], Kelly Sullivan[1], Amber Miller[1], Israt Jahan[1] & Theresa Zesiewicz[1*]

[1] Department of Neurology, University of South Florida College of Medicine, Parkinson's Disease and Movement Disorders Center, Tampa, Florida, United States of America, [2] UF Center for Movement Disorders and Neurorestoration, Gainesville, Florida, United States of America, [3] Department of Neurosurgery and Brain Repair, University of South Florida College of Medicine, Parkinson's Disease and Movement Disorders Center, Tampa, Florida, United States of America

Abstract

Background: Deep brain stimulation (DBS) is an increasingly utilized therapeutic modality for the management of medication refractory essential tremor (ET). The aim of this study was to determine whether DBS allowed for anti-tremor medication reduction within the year after the procedure was performed.

Methods: We conducted a retrospective chart review and telephone interviews on 34 consecutive patients who had been diagnosed with ET, and who had undergone unilateral DBS surgery.

Results: Of the 34 patients in our cohort, 31 patients (91%) completely stopped all anti-tremor medications either before surgery (21 patients, 62%) or in the year following DBS surgery (10 patients, 29%). Patients who discontinued tremor medications before DBS surgery did so because their tremors either became refractory to anti-tremor medication, or they developed adverse events to tremor medications. Patients who stopped tremor medications after DBS surgery did so due to sufficient tremor control. Only three patients (9%) who were taking tremor medications at the time of surgery continued the use of a beta-blocker post-operatively for the purpose of hypertension management in all cases.

Discussion: The data from this study indicate that medication cessation is common following unilateral DBS for ET.

Keywords: Essential tremor, medications, deep brain stimulation, adverse events

Citation: Resnick AS, Okun MS, Malapira T, et al. Sustained medication reduction following unilateral VIM thalamic stimulation for essential tremor. Tremor Other Hyperkinet Mov 2012;2: http://tremorjournal.org/article/view/38

*To whom correspondence should be addressed. E-mail: tzesiewi@health.usf.edu

Editor: Elan D. Louis, Columbia University, United States of America

Received: May 21, 2011 **Accepted:** July 26, 2011 **Published:** April 6, 2012

Copyright: © 2012 Resnick et al. This is an open-access article distributed under the terms of the Creative Commons Attribution–Noncommercial–No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original author(s) and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: None.

Competing Interests: The authors report no conflict of interest.

Introduction

Essential Tremor (ET) is a progressive, neurological disorder that is characterized by postural, intention, and kinetic tremor.[1–3] It is estimated that more than 10 million people in the United States suffer from ET.[4–6] Medication therapy is often used to control and mitigate symptoms, although medications may not prove efficacious in many cases.[7,8]

Deep brain stimulation (DBS) is an increasingly and commonly utilized therapeutic modality that is thought to work by disrupting a cerebello-thalamic-cortical loop that has been implicated in the genesis of the abnormal oscillation.[9–11] DBS has a higher magnitude of effect in treating ET than medications, although it may be associated with infrequent but more serious side effects. The primary aim of this study was to evaluate whether anti-tremor medications could be reduced or discontinued in the year following DBS surgery for the management of ET.

Methods

Consecutive subjects from the University of South Florida (USF) Parkinson's Disease and Movement Disorders Center were identified using an Institutional Review Board-approved protocol. A query of the center's electronic database was performed to identify patients with a diagnosis of ET. Charts were individually reviewed to assess eligibility criteria, which included 1) a unilateral thalamic DBS device implanted between October 2000 through October 2010 (Medtronic Activa

Table 1. Anti-tremor Medications Taken by All Patients within the Year Prior to Deep Brain Stimulation (DBS) Surgery.

	Primidone Only	Propranolol Only	Topiramate Only	Primidone, Propranolol, and Topiramate	Primidone and Propranolol Only	Other Therapy
Short Disease Duration[1]	2	2	0	5	0	2
Long Disease Duration[2]	7	4	0	10	2	0

[1]Number of patients taking medication prior to DBS surgery (n=11).
[2]Number of patients taking medication prior to DBS surgery (n=23).

Therapy, Minneapolis, Minnesota); 2) a diagnosis of ET made by a movement disorders specialist (T.A.Z.); 3) the indication for DBS surgery to alleviate tremor in the dominant hand, or, alternatively, to alleviate tremor in the more affected hand; 4) the following of each patient at our center for programming/medication management.

Each patient's electronic chart was reviewed for specific variables: anti-tremor medications taken 1 year before (Table 1) and 1 year after the DBS surgery, date of DBS surgery, current age, age at time of surgery, disease duration at time of surgery, sex, family history, confirmation of unilateral implantation, and severity of tremor. Subjective variables such as improvement in sleep patterns and overall cognition were also asked during patient interview. Subjects were then classified into two categories based upon the length of time diagnosed with ET: long disease duration (LDD: $\geqslant$10 years) and short disease duration (SDD: $<$10 years). Within each category, patients were then further classified into those who 1) were refractory to anti-tremor medications (patients whose tremor became resistant or unresponsive to such medications even at maximally tolerated doses) and ceased their use prior to surgery, 2) experienced adverse events from taking anti-tremor medications and who also ceased their use prior to surgery, and 3) had derived benefit from anti-tremor medications and therefore continued to take them at the time of their surgery.

Results

Forty-four patients were identified in the initial chart review and 10 of these patients (23%) were excluded from the study because they were either not followed at our center for DBS programming/medication management (seven patients, 16%), or they were deceased (three patients, 7%). Data from 34 patients was reviewed. The mean age of patients in the study was 76 $\pm$ 16.2 years (range 35–89 years) and 23 patients (68%) were male. The mean age at the time of DBS surgery was 70 $\pm$ 18.1 years (range 35–89 years) and the mean age at time of diagnosis was 49 $\pm$ 22.7 years (range 10–80 years). Twelve patients (35%) reported a family history of tremor. Thirty-one of the 34 patients (91%) received left-sided ventral intermediate nucleus (VIM) DBS implantation for tremor management; three left-handed patients were implanted on the right side (9%). All patients had tremor that was regarded by their evaluating physicians as "severe." Twenty-three patients (68%) had been diagnosed with ET for a period of 10 years or more (LDD group, mean 21 years) prior to their date of DBS surgery (range 10–51 years). All patients had previously experienced efficacy from medications, however medication benefit waned.

Of the 34 patients in the cohort, 31 patients (91%) completely stopped all anti-tremor medications before or after surgery (Figure 1). Twenty-one (62%) of 31 patients stopped medication before surgery, either because their tremors became refractory to anti-tremor medication or because they developed adverse events to tremor medications. Ten (29%) of 31 patients stopped medications in the year after DBS due to sufficient tremor control. Three patients (9%) who were taking tremor medications at the time of surgery continued the use of a beta-blocker post-operatively for the purpose of hypertension management.

When evaluating the cohort with respect to duration of ET, 17 of 23 patients (74%) with LDD ET stopped anti-tremor medication(s) (primidone, propranolol, and topiramate) at least 1 year prior to DBS surgery. Of these, 13 patients stopped anti-tremor medications due to lack of efficacy, while four patients discontinued anti-tremor medications due to adverse events. Of the 11 patients who had a diagnosis of ET for a period of less than 10 years (SDD group), four of them (36%) stopped anti-tremor medications at least 1 year prior to DBS due to side effects of anti-tremor medications during upward titration of dosage(s).

Thirty patients (88%) reported subjective improvement in sleep patterns throughout the night and 29 patients (85%) reported an overall improvement in their general cognitive state when combining DBS with the discontinuation of anti-tremor medications. Further details regarding discontinuation of anti-tremor medications before and after DBS surgery are reported in Figure 1.

Discussion

DBS is now widely utilized for the treatment of many medication-refractory movement disorders. The primary goal of the study was to evaluate how DBS for ET would impact use of anti-tremor medications following DBS. Our findings indicate that approximately three-quarters of ET patients who underwent DBS and who had not previously terminated anti-tremor medications eventually stopped taking anti-tremor medications within the year following DBS surgery. The main reason for termination of previous anti-tremor pharmacotherapy post-operatively was successful reduction or complete abolition of tremor from DBS surgery. The study also found that

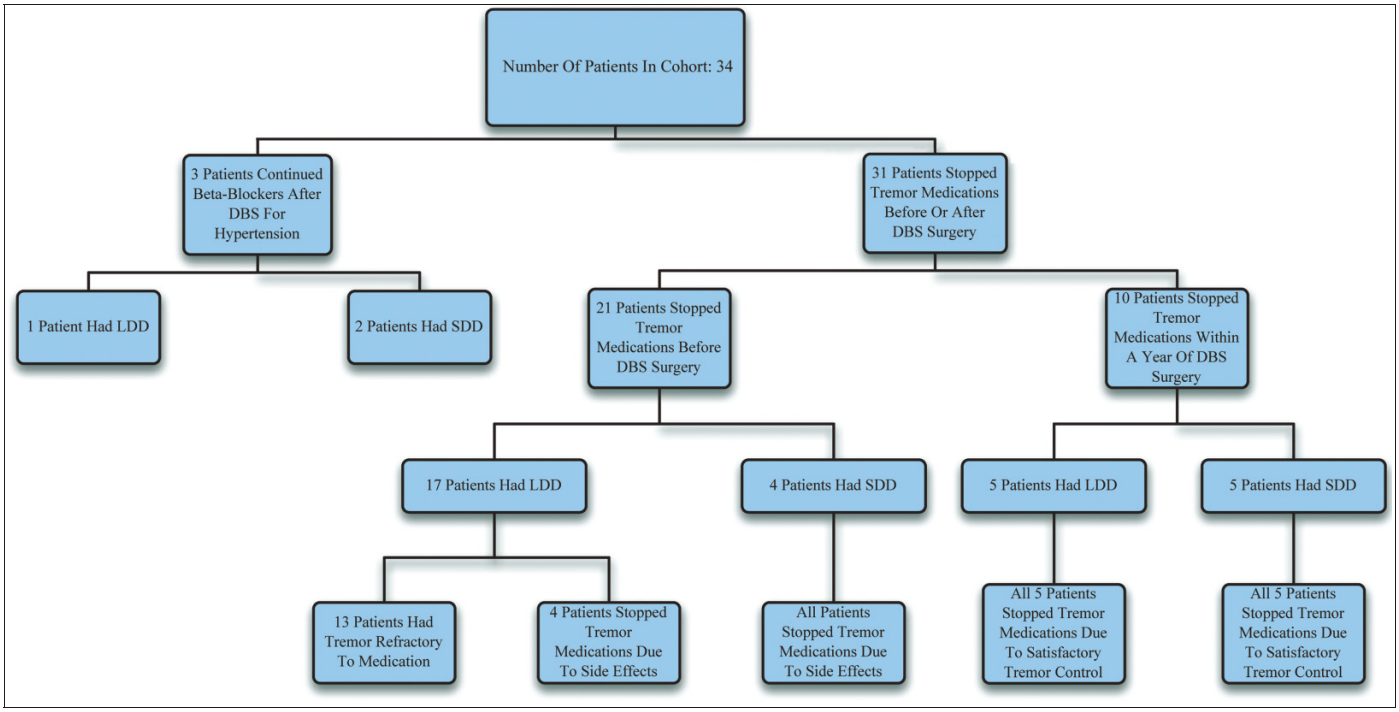

Figure 1. Quantitative breakdown of tremor medication usage among patients. DBS, deep brain stimulation; LDD, long disease duration; SDD, short disease duration.

Table 2. Pub-Med Literature Review Documenting Various Studies Relating Essential Tremor (ET) and Deep Brain Stimulation (DBS).

Author	Number of Patients (n)	Year	Target	Reduction in Medication? If so, by what amount?	Outcome of Study
Barbe, et al.[32]	23	2010	VIM	Not detailed	ADLs improved significantly and optimal stimulation parameters in ET patients led to initial short-term improvement that adjusted over time.
Flora, et al.[33]	430	2010	VIM	Not detailed	"…[medication] treatments have limited success and can become ineffective over time. For medication-refractory patients, alternative treatment is limited to thalamotomy or DBS."
Blomstedt, et al.[34]	21	2010	Posterior subthalamic area	Not detailed	ADLs improved by 66% and stimulation at this target resulted in significant tremor reduction.
Lyons, et al.[23]	Not indicated	2003	VIM	Not detailed	Reports that current tremor medications are effective in 50% of patients. Also reports that surgical options for tremor are effective in 90% of patients.
Fields, et al.[35]	40	2003	VIM	Not detailed	DBS improved quality of life outcomes, cognition, and mood. Anxiety was also improved.
Perlmutter, et al.[36]	Not indicated	2002	VIM	Not detailed	Increased blood flow shows that DBS "stimulates and does not inactivate projection neurons in VIM thalamus."

Table 2. Continued

Author	Number of Patients (n)	Year	Target	Reduction in Medication? If so, by what amount?	Outcome of Study
Koller, et al.[37]	49	2001	VIM	Not detailed	Unilateral DBS of the thalamus is efficacious for a portion of ET patients, however this is compromised by device complications.
Pahwa et al.[38]	35	2001	VIM	Not detailed	Thalamotomy has a higher rate of complications and DBS should be chosen over thalamotomy when considering surgical treatment.
Koller, et al.[39]	Not indicated	2000	VIM	Not detailed	DBS is highly effective for the treatment of tremor and is preferred to thalamotomy.
Pahwa, et al.[40]	Not indicated	2000	VIM	Not detailed	Thalamotomy and DBS are stereotactic procedures that aid in the treatment of ET. While both are associated with morbidities, medication-refractory patients can be candidates for both Not Mentioned procedures.
Tröster et al.[41]	40	1999	VIM	Not detailed	Unilateral DBS of the thalamus for ET is considered safe and associated with anxiety and quality of life improvements.
Pahwa, et al.[42]	9	1999	VIM	Not detailed	Bilateral DBS is effective in improving tremor and disability in patients with ET, however, dysarthria can be an adverse effect of the stimulation.
Koller, et al.[43]	29 (Diagnosed with ET)	1997	VIM	Not detailed	High-frequency stimulation for ET and parkinsonian tremor patients is well tolerated, highly effective, and had only mild adverse effects.
Hubble, et al.[44]	10	1996	VIM	Not detailed	DBS is considered to be safe and effective in its reduction of tremor and disability in patients with ET.
Lyons, et al.[45]	Not indicated	2008	VIM	Not detailed	DBS is effective in treating medication-refractory and disabling ET. Surgical complications are typically uncommon.
Pahwa, et al.[46]	26 (Diagnosed with ET)	2006	VIM	Not detailed	DBS for long-term management of ET is safe and considered to be effective. Bilateral stimulation is associated with dysarthria incoordination.
Graff-Radford, et al.[47]	31	2010	VIM	Not detailed	Tremor rating scale subscale scores improved for all unilateral and bilateral VIM DBS patients. Subscale scores for visual analog mood scale varied for unilateral and bilateral DBS patients.
Ondo, et al.[48]	73	2001	VIM	Not detailed	Tremor on contralateral side "improved significantly and robustly in PD and ET" after VIM DBS. Tremor was not worsened on ipsilateral side, but rather mildly improved in ET patients.

Abbreviations: ADLs, activities of daily living; PD, Parkinson's disease; VIM, ventral intermediate nucleus.

anti-tremor medications are less effective in long duration ET (≥10 years) than in short duration ET (<10 years).

Pharmacological effects in patients with ET have been previously characterized by several studies.[8,13–22] Lyons et al.[24] found that anti-tremor medications were limited in their ability to control tremor, and only effectively treated tremor in half of ET patients.[12,23,] In contrast, DBS has been reported to result in a 60–90% reduction in tremor amplitude.[25] Side effects from DBS, however, may be more serious. Table 2 summarizes major studies of DBS and/or pharmacotherapy for ET.

Propranolol and primidone have been identified as the two main pharmacological therapies for treatment of ET and authors have generally reported that their use results in a reduction of tremor by half in 50% of patients.[23] Propranolol, despite being used solely for tremor, is also an effective therapy for the treatment of hypertension and other cardiac issues, however, depression, low blood pressure, and other cognitive issues have been associated with its use.[14,26,27] Three patients in our cohort who discontinued anti-tremor medications within 1 year following DBS surgery continued on a beta-blocker with the cited indication being hypertension (two patients from the LDD group and one patient from the SDD group). An important limitation to the current study was that propranolol may have provided a symptomatic effect in these patients and inflated their improvement scores following DBS.[28] Additionally, small sample size, retrospective nature of the study, and data obtained only by a telephone interview and patient chart review (not in a clinical setting) were other limitations in our study.

There are economic and symptomatic benefits for medication discontinuation, particularly primidone, which has been reported to be associated with lethargy and cognitive issues in addition to difficulty with tolerance and upward titration.[29–31] Thus, medication discontinuation post-DBS may result in improved cognition, reduction of side effects, and improved sleep patterns. However, despite these benefits, practitioners should be aware that medication reduction could have a symptomatic price, particularly on the contralateral extremity in the case of unilateral VIM DBS. Although our study did not specifically address bilateral VIM DBS, which is associated with more side effects (e.g. speech, gait), it is interesting that medication reduction occurred at such a high prevalence.

Our cohort found that discontinuation of medications for ET patients post-DBS was common. As neuromodulation therapy evolves for ET, it will be the responsibility of the practitioner to carefully choose the proper treatment for each patient, whether pharmacological or surgical. Future research studies should include long-term studies on the use of medication therapy following DBS surgery, including patients with bilateral stimulation. Recognizing that each patient is unique will be a critical step in optimizing outcomes.

References

1. Louis ED. Essential tremor. *Arch Neurol* 2000;57:1522–1524, http://dx.doi.org/10.1001/archneur.57.10.1522.

2. Zesiewicz TA, Chari A, Jahan I, Miller AM, Sullivan KL. Overview of essential tremor. *Neuropsychiatr Dis Treat* 2010;6:401–408, http://dx.doi.org/10.2147/NDT.S4795.

3. Benito-Leon J. How common is essential tremor? *Neuroepidemiology* 2009;32:215–216, http://dx.doi.org/10.1159/000195692.

4. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 2010;25:534–541, http://dx.doi.org/10.1002/mds.22838.

5. Jankovic J. Essential tremor: clinical characteristics. *Neurology* 2000;54:S21–25.

6. Pahwa R, Lyons KE. Essential tremor: differential diagnosis and current therapy. *Am J Med* 2003;115:134–142.

7. Diaz NL, Louis ED. Survey of medication usage patterns among essential tremor patients: movement disorder specialists vs. general neurologists. *Parkinsonism Relat Disord* 2010;16:604–607, http://dx.doi.org/10.1016/j.parkreldis.2010.07.011.

8. Louis ED, Rios E, Henchcliffe C. How are we doing with the treatment of essential tremor (ET)?: Persistence of patients with ET on medication: data from 528 patients in three settings. *Eur J Neurol* 2010;17:882–884.

9. Morishita T, Foote KD, Wu SS, et al. Brain penetration effects of microelectrodes and deep brain stimulation leads in ventral intermediate nucleus stimulation for essential tremor. *J Neurosurg* 2010;112:491–496, http://dx.doi.org/10.3171/2009.7.JNS09150.

10. Resnick AS, Foote KD, Rodriguez RL, et al. The number and nature of emergency department encounters in patients with deep brain stimulators. *J Neurol* 2010;257:122–131.

11. Skidmore FM, Rodriguez RL, Fernandez HH, et al. Lessons learned in deep brain stimulation for movement and neuropsychiatric disorders. *CNS Spectr* 2006;11:521–536.

12. Lyons KE, Pahwa R. Pharmacotherapy of essential tremor : an overview of existing and upcoming agents. *CNS Drugs* 2008;22:1037–1045, http://dx.doi.org/10.2165/0023210-200822120-00006.

13. Schadt CR, Duffis EI, Charles PD. Pharmacological treatment of disabling tremor. *Expert Opin Pharmacother* 2005;6:419–428, http://dx.doi.org/10.1517/14656566.6.3.419.

14. Koller WC, Hristova A, Brin M. Pharmacologic treatment of essential tremor. *Neurology* 2000;54:S30–38.

15. Lorenz D, Deuschl G. Update on pathogenesis and treatment of essential tremor. *Curr Opin Neurol* 2007;20:447–452, http://dx.doi.org/10.1097/WCO.0b013e3281e66942.

16. Murray TJ. Treatment of essential tremor with propranolol. *Can Med Assoc J* 1972;107:984–986.

17. Ondo WG. Essential tremor: treatment options. *Curr Treat Options Neurol* 2006;8:256–267, http://dx.doi.org/10.1007/s11940-006-0016-8.

18. Sasso E, Perucca E, Fava R, Calzetti S. Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990;13:67–76, http://dx.doi.org/10.1097/00002826-199002000-00007.

19. Tolosa ES, Loewenson RB. Essential tremor: treatment with propranolol. *Neurology* 1975;25:1041–1044.

20. Zesiewicz TA. Low-dose topiramate (topamax) in the treatment of essential tremor. *Clin Neuropharmacol* 2007;30:247–248.

21. Zesiewicz TA, Ward CL, Hauser RA, et al. Pregabalin (Lyrica) in the treatment of essential tremor. *Mov Disord* 2007;22:139–141, http://dx.doi.org/10.1002/mds.21211.

22. Koller W, Herbster G, Cone S. Clonidine in the treatment of essential tremor. *Mov Disord* 1986;1:235–237, http://dx.doi.org/10.1002/mds.870010403.

23. Lyons KE, Pahwa R, Comella CL, et al. Benefits and risks of pharmacological treatments for essential tremor. *Drug Saf* 2003;26:461–481, http://dx.doi.org/10.2165/00002018-200326070-00003.

24. Lyons KE, Pahwa R. Deep brain stimulation and essential tremor. *J Clin Neurophysiol* 2004;21:2–5, http://dx.doi.org/10.1097/00004691-200401000-00002.

25. Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005;64:2008–2020, http://dx.doi.org/10.1212/01.WNL.0000163769.28552.CD.

26. Farias AQ, Kassab F, da Rocha EC, et al. Propranolol reduces variceal pressure and wall tension in schistosomiasis presinusoidal portal hypertension. *J Gastroenterol Hepatol* 2009;24:1852–1856, http://dx.doi.org/10.1111/j.1440-1746.2009.05912.x.

27. Punda A, Polic S, Rumboldt Z, et al. Effects of atenolol and propranolol on platelet aggregation in moderate essential hypertension: randomized crossover trial. *Croat Med J* 2005;46:219–224.

28. Louis ED, Benito-Leon J, Bermejo-Pareja F. Antihypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES). *Neuroepidemiology* 2009;33:286–292, http://dx.doi.org/10.1159/000235641.

29. O'Suilleabhain P, Dewey RB, Jr. Randomized trial comparing primidone initiation schedules for treating essential tremor. *Mov Disord* 2002;17:382–386, http://dx.doi.org/10.1002/mds.10083.

30. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol* 2011;10:148–161, http://dx.doi.org/10.1016/S1474-4422(10)70322-7.

31. Gironell A, Kulisevsky J. Diagnosis and management of essential tremor and dystonic tremor. *Ther Adv Neurol Disord* 2009;2:215–222, http://dx.doi.org/10.1177/1756285609104791.

32. Barbe MT, Liebhart L, Runge M, et al. Deep brain stimulation in the nucleus ventralis intermedius in patients with essential tremor: habituation of tremor suppression. *J Neurol* 2010;258(3):434–439.

33. Flora ED, Perera CL, Cameron AL, Maddern GJ. Deep brain stimulation for essential tremor: a systematic review. *Mov Disord* 2010;25:1550–1559, http://dx.doi.org/10.1002/mds.23195.

34. Blomstedt P, Sandvik U, Tisch S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Mov Disord* 2010;25:1350–1356, http://dx.doi.org/10.1002/mds.22758.

35. Fields JA, Troster AI, Woods SP, et al. Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor. *J Neurol Neurosurg Psychiatry* 2003;74:305–311, http://dx.doi.org/10.1136/jnnp.74.3.305.

36. Perlmutter JS, Mink JW, Bastian AJ, et al. Blood flow responses to deep brain stimulation of thalamus. *Neurology* 2002;58:1388–1394.

37. Koller WC, Lyons KE, Wilkinson SB, et al. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord* 2001;16:464–468, http://dx.doi.org/10.1002/mds.1089.

38. Pahwa R, Lyons KE, Wilkinson SB, et al. Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. *Mov Disord* 2001;16:140–143, http://dx.doi.org/10.1002/1531-8257(200101)16:1<140::AID-MDS1025>3.0.CO;2-T.

39. Koller WC, Pahwa PR, Lyons KE, Wilkinson SB. Deep brain stimulation of the Vim nucleus of the thalamus for the treatment of tremor. *Neurology* 2000;55:S29–33.

40. Pahwa R, Lyons K, Koller WC. Surgical treatment of essential tremor. *Neurology* 2000;54:S39–44.

41. Troster AI, Fields JA, Pahwa R, et al. Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. *Neurology* 1999;53:1774–1780.

42. Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology* 1999;53:1447–1450.

43. Koller WC. Essential tremor: the beginning of a new era. *Mov Disord* 1997;12:841, http://dx.doi.org/10.1002/mds.870120602.

44. Hubble JP, Busenbark KL, Wilkinson S, et al. Deep brain stimulation for essential tremor. *Neurology* 1996;46:1150–1153.

45. Lyons KE, Pahwa R. Deep brain stimulation and tremor. *Neurotherapeutics* 2008;5:331–338, http://dx.doi.org/10.1016/j.nurt.2008.01.004.

46. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg* 2006;104:506–512, http://dx.doi.org/10.3171/jns.2006.104.4.506.

47. Graff-Radford J, Foote KD, Mikos AE, et al. Mood and motor effects of thalamic deep brain stimulation surgery for essential tremor. *Eur J Neurol* 2010;17:1040–1046.

48. Ondo W, Dat Vuong K, Almaguer M, et al. Thalamic deep brain stimulation: effects on the nontarget limbs. *Mov Disord* 2001;16:1137–1142, http://dx.doi.org/10.1002/mds.1249.