

Current clinical application of deep-brain stimulation for essential tremor

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Background: Deep-brain stimulation (DBS) is an established treatment for medically refractory essential tremor (ET). This article reviews the current evidence supporting the efficacy and safety of DBS targets, including the ventral intermediate (VIM) nucleus and posterior subthalamic area (PSA) in treatment of ET.

Methods: A structured PubMed search was performed through December 2012 with keywords “deep brain stimulation (DBS),” “essential tremor (ET),” “ventral intermediate (VIM) nucleus,” “posterior subthalamic area (PSA),” “safety,” and “efficacy.”

Results: Based on level IV evidence, both VIM and PSA DBS targets appear to be safe and efficacious in ET patients in tremor reduction and improving activities of daily living, though the literature on PSA DBS is limited in terms of bilateral stimulation and long-term follow-up. DBS-related adverse effects are typically mild and stimulation-related. Hardware-related complications after DBS may not be uncommon, and often require additional surgical procedures. Few studies assessed quality-of-life and cognition outcomes in ET patients undergoing DBS stimulation.

Conclusion: DBS appears to be a safe and effective treatment for medically refractory ET. More systematic studies comparing VIM and PSA targets are needed to ascertain the most safe and effective DBS treatment for medically refractory ET. More research is warranted to assess quality-of-life and cognition outcomes in ET patients undergoing DBS.

Keywords: deep-brain stimulation (DBS), essential tremor (ET), ventral intermediate (VIM) nucleus, posterior subthalamic area (PSA), safety, efficacy

Introduction

Essential tremor (ET) is the most common movement disorder, and is characterized by 4–12 Hz postural and kinetic tremor involving the arms and less commonly the head, lower extremities, and voice.¹ The estimated prevalence of ET is 0.4%–3.9%,² with even higher prevalence (4.6%) in people over 65 years of age.³ ET symptoms, thought to be benign in nature, often cause embarrassment and can potentially lead to serious disability in a subset of ET patients.^{4,5}

The first-line treatment of ET is pharmacologically based and comprised of trials of medications, including propranolol and primidone,⁶ though these medications tend to lose efficacy over time and are limited by adverse effects.¹ Second-line treatments include trial of additional pharmacological agents, including anticonvulsants, neuroleptics, antidepressants, and botulinum toxin.⁶ Overall, the best medication outcomes tend to show tremor reduction in only approximately 50% of ET patients.⁷

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Once medical treatments fail, ET patients are considered for surgical treatments, including stereotactic standard thalamotomy, gamma-knife thalamotomy, and deep-brain stimulation (DBS). During the performance of thalamotomies for ET in the 1960s, investigators found that intraoperative high-frequency stimulation (100 Hz) of the ventral intermediate (VIM) nucleus of the thalamus dramatically reduced tremor,^{8,9} which eventually led to clinical application of thalamic DBS in treatment of ET by Benabid and colleagues.¹⁰

Currently, DBS is a US Food and Drug Administration (FDA)-approved treatment for management of medically refractory ET. The DBS system comprises three components: implanted pulse generator, lead, and an extension. Despite the established efficacy of DBS in treatment of ET over the last two decades, the exact mechanism of action of DBS remains unclear.¹¹ The efficacy of DBS has been

noted to be comparable to thalamotomy;¹² however, DBS has essentially replaced ablation surgical procedures, due to its efficacy, safety, and relative reversibility of the adverse effects in the treatment of ET.¹³

For treatment of medically refractory ET, the VIM nucleus of the thalamus is the most common DBS target, whereas evidence is growing to support the efficacy of DBS of the posterior subthalamic area (PSA). This article reviews the systematic evidence focusing on efficacy and safety outcomes of VIM and PSA targets in DBS treatment of medically refractory ET.

Methods

A structured PubMed search was performed through December 2012 with the keywords “deep brain stimulation (DBS),” “essential tremor (ET),” “ventral intermediate (VIM) nucleus,” “posterior subthalamic area (PSA),” “safety,” and

Table I Efficacy outcomes of VIM DBS in essential tremor

Study	ET patients (n)	Target	Follow-up	Outcome/improvement
Carpenter et al ¹⁴	n = 7	5 unilateral, 2 bilateral VIM	18 months	DBS on/off; 4/7 patients showed reduction in voice tremor
Lyons et al ¹⁵	n = 22	Unilateral VIM	11 months	DBS on/off; 57.9% (self-rated TADLS), 39.3% (overall tremor) ($P < 0.001$)
Koller et al ¹⁶	n = 38	Unilateral VIM	3, 6, 12 months	DBS on/off; 75% (head tremor); significantly improved overall tremor ($P < 0.01$)
Obwegeser et al ¹⁷	n = 27	14 unilateral and 13 bilateral VIM	12 months	DBS on/off; unilateral – 82% (arm), 38% (head), voice none; bilateral – 95% (head), 83% (voice)
Koller et al ¹⁸	n = 49	Unilateral VIM	40.2 ± 14.7 months	DBS on/off; 78.5% (overall tremor) ($P < 0.01$)
Hariz et al ¹⁹	n = 27	Unilateral and bilateral VIM	12.5 months	DBS before/after; 47.4% (tremor) ($P < 0.0001$)
Sydow et al ²⁰	n = 19	12 unilateral and 7 bilateral VIM	6 years	DBS on/off; significant improvement in overall tremor and ADL ($P < 0.001$); no improvement in voice tremor
Rehncrona et al ²¹	n = 19	17 unilateral and 2 bilateral VIM	78 months	47.1% (overall tremor)
Putzke et al ²²	n = 22	29 unilateral and 23 bilateral VIM	1, 3, 12 months; 2 and 3 years	DBS on/off; significant improvement in overall tremor and ADL ($P < 0.05$)
Lee and Kondziolka ²³	n = 19	Unilateral VIM	27 months	DBS before/after; 75.8% (tremor) and 64.3% (handwriting) ($P < 0.005$)
Pahwa et al ²⁴	n = 26	18 unilateral and 8 bilateral VIM	5 years	DBS on/off; unilateral – 75% (contralateral arm); bilateral – 65% (left arm), 85% (right arm); ($P < 0.01$)
Blomstedt et al ²⁵	n = 19	Unilateral VIM	86 ± 9 months	DBS before/after; 60.3% (hand tremor), 35.4% (hand function)
Pilitsis et al ²⁶	n = 26	22 unilateral and 4 bilateral	40 months	DBS before/after; 75.3% (tremor), 73.8% (handwriting)
Zhang et al ²⁷	n = 34	23 unilateral and 11 bilateral VIM	56.9 months	DBS before/after; 80.4% (tremor) and 69.7% (handwriting) ($P < 0.001$)
Nazzaro et al ²⁸	n = 91	Unilateral VIM	9 years	DBS before/after; 31% (tremor), 36.9% (ADL), 10.3% (QOL at 4 years)
de Oliveira et al ²⁹	n = 26	19 unilateral and 7 bilateral VIM	41 months	DBS on/off; significant improvement in overall tremor and QOL

Abbreviations: ET, essential tremor; VIM, ventrointermediate nucleus of thalamus; ADL, activities of daily living; TADLS, tremor activities of daily living scale; QOL, quality of life; DBS, deep-brain stimulation.

Table 2 Efficacy outcomes of PSA DBS in essential tremor

Study	ET patients (n)	Target	Follow-up	Outcome/improvement
Murata et al ³⁰	n = 8	Unilateral Zi and prelemniscal radiation	42 months	81% (contralateral tremor)
Plaha et al ³¹	n = 4	Bilateral PSA	12 months	DBS before/after; 80% (tremor)
Blomstedt et al ³²	n = 21	PSA; 19 unilateral and 2 bilateral	1 year	DBS before/after and DBS on/off; 95% (upper-extremity tremor); 87% (hand function); 66% (ADL)
Plaha et al ³³	n = 15	cZi; bilateral	31.7 ± 28.6 months	DBS before/after and DBS on/off; 73.8% (overall tremor); 60.1% (hand function); 80% (ADL); 23.7% (QOL)
Blomstedt et al ³⁴	n = 5; previously failed VIM	cZi	1–2 years	57% (cZi) versus 25% (VIM)
Fytagoridis et al ³⁵	n = 18	cZi; 16 unilateral and 2 bilateral	4 years	DBS before/after and DBS on/off; 51.4% (total tremor); 89.4% (upper-extremity tremor); 78% (hand function)
Sandvik et al ³⁶	n = 16	cZi; 14 unilateral and 2 bilateral	12 months	DBS before/after; 95% (tremor); 78% (hand function); 71% (ADL); nonsignificant for modest changes in QOL

Abbreviations: ET, essential tremor; PSA, posterior subthalamic area; cZi, caudal zona incerta; VIM, ventrointermediate nucleus of thalamus; ADL, activities of daily living; QOL, quality of life; DBS, deep-brain stimulation; Zi, zona incerta.

“efficacy”. In this review, we have included original research studies published in the English medical literature focusing on DBS treatment in ET patients only. A total of 17 studies for VIM DBS^{14–29} and seven studies for PSA DBS^{30–36} were included in this review.

Results

Tables 1 and 2 summarize the studies assessing efficacy outcomes of VIM and PSA DBS targets in medically refractory ET patients.

Discussion

Ventral intermediate nucleus of thalamus DBS

Based on direct and indirect neurophysiological studies, it has been suggested that a neuronal network involving the thalamus (especially VIM), the sensorimotor cortex, the inferior olivary nuclei, and cerebellum may be responsible in the production of ET.³⁷ Animal studies further support this hypothesis, as harmaline, a central nervous stimulant, has been used to induce a reversible essential tremor-like state characterized by abnormal tremor-specific oscillations in the olivocerebellar pathway.³⁷

VIM is thought to correspond to the ventral lateral posterior nucleus (VLp) in the nomenclature used in the animal literature.³⁸ According to animal studies, VLp has been shown to have connectivity to the primary motor cortex³⁹ and to receive cerebellar input,⁴⁰ and these findings have been replicated in human subjects using noninvasive diffusion tactography.⁴¹

The posterior part of the ventral lateral anterior nucleus (VLa), which lies directly anterior to the VLp, receives pallidal afferents.⁴¹ Given their close proximity, it is likely that stimulation of the VLa may contribute to modulation of the tremor network in VIM DBS.⁴¹

VIM DBS appears to be an essentially safe treatment, with few serious adverse events likely not affecting its long-term outcomes.⁴² VIM DBS is considered to be the surgical target of choice for treatment of medically refractory ET.⁷ The optimal electrode location for DBS in ET corresponds to the anterior margin of the VIM. It has been suggested that leads located >2 mm (in the plane of the commissures) from the optimal coordinates are more likely to be associated with poor tremor control than leads <2 mm from the optimal location.⁴³

The authors have reported postsurgical follow-up duration for VIM DBS patients ranging from 3 months to a maximum of 9 years. Change in the Fahn–Tolosa–Marin (FTM) tremor-rating scale score is the primary outcome measure in most of these studies, except for two studies using the essential tremor-rating scale (ETRS) as the primary outcome measure.^{20,21} The assessors reportedly did blinded assessments only in five of 17 studies.^{15,16,18,19,21}

In this review, the authors report significant improvement (40%–85%) in overall ET symptoms postoperatively, with these improvements being generally sustained during long-term follow-up after VIM DBS. Where reported, significant improvement in tremor-rating scores (FTM/ETRS) was noted with DBS switched on compared to

scores with DBS off and with the baseline measurements. Significant improvement in hand function, handwriting, and activities of daily living has been noted in ET, along with improvement in tremor symptoms, after VIM DBS in the majority of studies.^{15,16,20,22,23,26–28} Sustained improvements in quality-of-life (QOL) outcomes and patient satisfaction at long-term follow-up after VIM DBS have been assessed in four of 17 studies.^{19,27–29} One of the studies assessing QOL outcomes suggests that patient satisfaction may be directly proportional to improvements in activities of daily living and tremor control in ET patients undergoing VIM DBS.²⁹

The effect of VIM DBS specifically on head-tremor symptoms has been established in two of 17 studies,^{16,17} with bilateral VIM DBS being more effective than unilateral stimulation in one study.¹⁷ Voice-tremor outcomes in ET patients after VIM DBS stimulation seem to be somewhat mixed. According to one study including seven ET patients (five unilateral, two bilateral VIM DBS), voice tremor improved significantly only in patients who had severe symptoms, and there were no notable differences between patients who underwent unilateral versus bilateral VIM DBS.¹⁴ Significant improvement in voice tremor (83%) in patients undergoing bilateral VIM DBS stimulation compared to unilateral stimulation was observed in another study,¹⁷ whereas no improvement in voice tremor was noted in 19 ET patients (twelve unilateral, seven bilateral) postoperatively and at 6 years after VIM DBS stimulation in another.²⁰

The most common adverse events associated with VIM DBS include paresthesias, dysarthria, and disequilibrium. These side effects are typically mild and generally amenable to changes in DBS parameters. Dysarthria and disequilibrium have been more commonly associated with bilateral VIM DBS stimulation. Serious adverse events, such as stroke and seizures, have been reported occasionally after VIM DBS surgery. DBS device-related complications, including infection, lead fracture, and skin erosion, were not uncommon and often required further surgery, thus increasing the health care and cost burden of the DBS procedure. One of the studies has reported the overall hardware-related complication rate to be 23.5%.²⁷

Posterior subthalamic area DBS

Another emerging DBS target for ET, PSA, is bound anteriorly by the posterior border of the subthalamic nucleus, superiorly by the ventral thalamic nuclei, inferiorly by the dorsal border of the substantia nigra, posteriorly by the medial lemniscus, posteromedially by the anterolateral border of the

red nucleus, posterolaterally by the ventrocaudal nucleus, and laterally by the posterior limb of the internal capsule.

PSA consists of the zona incerta (Zi) and prelemniscal radiation (Raprl). The Zi lies dorsal and posterior to the subthalamic nucleus (STN) and anatomically consists of a caudal part (cZi) and a rostral part. Its caudal or motor component lies posteromedial to the STN, and its rostral component extends over the dorsal and medial surface of the STN.^{44,45} The Raprl is a fiber bundle lying posterior to the STN, and separated from it by the intervening Zi. It contains fibers from the mesencephalic reticular formation that projects to the thalamus as well as ascending cerebellothalamic fibers.⁴⁶

The mechanism of tremor suppression by DBS in PSA (predominantly cZi) is not entirely clear.⁴⁶ The Zi is a heterogeneous nucleus that lies at the base of the dorsal thalamus and is considered to be an extension of the reticular/thalamic nucleus. It receives afferents from the globus pallidus internus, the substantia nigra reticulata (SNr),^{44,47,48} the ascending reticular activating system,^{47–49} the interpositus nucleus of the cerebellum, and also the motor, associative, and limbic areas of the cerebral cortex.⁴⁵ It sends efferents to the centromedian and parafascicular nuclei,^{50–52} the ventral anterior nucleus and the ventral lateral nucleus of the thalamus,⁵³ the midbrain extrapyramidal area and the medial reticular formation, the globus pallidus internus and substantia nigra reticulata,⁴⁴ the interpositus nucleus of the cerebellum, the inferior olive, and the cerebral cortex.^{54,55}

Abnormal synchronization of neuronal firing in the basal ganglia thalamocortical loop, the cerebellar thalamocortical loop, or both loops has been considered to be an underlying mechanism in a range of neurological disorders associated with tremor.⁵⁶ cZi proves to be an effective target for the surgical control of all forms of tremor, due to its unique GABAergic connections with both the basal ganglia and cerebellar thalamocortical loops. Additionally, stimulation of the Zi is likely to suppress the tremor by overriding the oscillations in the brain stem-motor effectors through which tremor oscillation may be transmitted.⁵⁶

In this review, PSA DBS has been targeted mainly in a unilateral fashion, with fewer patients undergoing bilateral stimulation. In five of seven studies,^{33–36} DBS targeting was more specific in the PSA region with stimulation of the caudal cZi only. The follow-up duration for PSA DBS patients ranges from 3 months to 4 years. Generally, PSA/cZi DBS stimulation has been associated with significant improvements in tremor (50%–95%) in both short-term and long-term follow-up. One study (n = 5) evaluating the efficacy of cZi DBS in patients with failed VIM DBS reported improvement in overall tremor

with cZi DBS (57%) compared to VIM DBS (25%), although considerable residual tremor was noted in patients with late failure of VIM.³⁴ Improvements in hand function and activities of daily living have been reported with PSA DBS in two of seven studies.^{32,35} The QOL outcomes with PSA DBS are somewhat mixed, as one study primarily including unilateral cZi target showed nonsignificant-to-modest improvements in QOL³⁶ compared to significant improvements associated with bilateral cZi stimulation.³³

The adverse effects associated with PSA DBS are usually mild, and include transient paresthesias, dysphasia, and disequilibrium. PSA DBS stimulation generally lacks lasting dysarthria and disequilibrium, in contrast to VIM DBS, particularly bilateral VIM DBS. This may be explained by the fact that the cZi DBS only overrides tremor oscillations without interrupting patterns of information related to fine movements of vocal cords and proprioceptive sensation.⁵⁶ Rare serious adverse events, including transient mild hemiparesis and seizure, have been reported with PSA DBS. Device-related complications such as infection have been less frequently reported with PSA DBS. However, it must be noted that the studies on PSA DBS in ET patients are still very limited compared to VIM DBS.

VIM versus PSA DBS

There are few studies comparing VIM and PSA targets for DBS treatment of ET. One retrospective study⁵⁷ including 36 ET patients (17 VIM/19 PSA) with 44 DBS electrodes reported that the electrode contact providing the best effect in individual tremor control, measured by the ETRS, was located predominantly in the Zi or Raprl (54%) compared to VIM (12%). Another prospective study including 68 ET patients (34 VIM/34 PSA) reported improvement in hand tremor and hand function (measured by ETRS) by 70% in the VIM group compared to 89% in the PSA group,⁵⁸ though the duration of follow-up varied between the two groups, with mean follow-up of 1 year for PSA DBS compared to 28 ± 24 months' follow-up for VIM DBS, and this may have potentially affected the outcomes. In this study, the efficacy of DBS in ET was not related to age, sex, or the severity of tremor, although patients with a more severe tremor at baseline had a higher degree of residual tremor on stimulation.

Additionally, PSA DBS has been proven to be effective in tremor suppression for those tremors difficult to be adequately controlled by VIM DBS, such as proximal postural tremor, distal intention tremor, and cerebellar outflow tremor associated with ET and multiple sclerosis.⁵⁸ However, to date,

there have been no randomized controlled trials comparing the safety and efficacy of VIM and PSA DBS in ET.

DBS patient selection for ET

All ET patients with medically refractory tremor should be considered for DBS after failed trials of medications that have proven to be effective in ET based on randomized controlled studies.¹¹ Elderly patients should be counseled about increased DBS-related surgical risks and their ability to consent for the procedure, particularly those with progressive memory dysfunction, should be investigated carefully.

Few studies report no overall change in cognitive functioning following VIM DBS. One study looking at cognitive outcomes in ET patients at 1-year follow-up reported no overall deleterious effects of unilateral VIM DBS on cognition, although preoperative verbal fluency diminution was noted be a predisposing factor toward further decline in verbal fluency after DBS.⁵⁹ In regard to impact of DBS of PSA region on cognition, a recent study reported a tendency toward an immediate and mostly transient postoperative decline in verbal fluency following cZi DBS for ET; however, this decline can be more pronounced and sustained over time in a subset of patients.⁶⁰ More systematic research is needed to assess the short- and long-term cognitive outcomes comparing unilateral and bilateral VIM/PSA DBS stimulation, particularly in elderly patients at higher risk of cognitive decline.

DBS treatment failure

DBS is generally an effective treatment for medically refractory ET, although treatment failure may occur in a subset of patients. Treatment failure may be seen in patients who receive no benefit immediately after surgery and those with good benefit initially, but tremor gradually returns after DBS surgery.²⁷ The initial nonresponse is more likely to be caused by suboptimal DBS electrode placement, and reimplantation of the DBS electrodes for optimal targeting should be considered in such cases.²⁷ The gradual loss of DBS effect over time is more complicated, and may be explained by progression of the ET and the phenomenon of tolerance. Given the slow progressive characteristics of ET and relatively stable stimulation-off symptoms even several years after DBS surgery, the role of disease progression in treatment failure after DBS is currently being debated.²⁷

Compared to PSA DBS, tolerance is not uncommon in ET patients undergoing VIM DBS, as evidenced by a gradual increase of DBS voltage (>3.6 V) during long-term programming.^{25,26,61} Strategies including lower DBS voltage settings and turning the DBS stimulator off during sleeping

hours might be helpful in patients experiencing tolerance.²⁵ Even thalamotomy may be considered as a salvage treatment option in some patients with loss of efficacy of DBS due to tolerance.⁶²

Conclusion

In summary, DBS of the VIM and PSA regions appears to be a safe and effective treatment for medically refractory ET. More systematic studies comparing VIM and PSA targets are needed to ascertain the most safe and effective DBS treatment for medically refractory ET. More studies are needed to assess QOL and cognition outcomes in ET patients undergoing DBS.

Disclosure

The authors report no conflicts of interest in this work.

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