EXPERT REVIEW OF NEUROTHERAPEUTICS, 2018
https://doi.org/10.1080/14737175.2018.1445526

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REVIEW

Surgical treatments for essential tremor

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ABSTRACT

Introduction: Essential tremor is the most common form of pathologic tremor. Surgical therapies disrupt tremorogenic oscillation in the cerebellothalamocortical pathway and are capable of abolishing severe tremor that is refractory to available pharmacotherapies. Surgical methods are raspidly improving and are the subject of this review.

Areas covered: A PubMed search on 18 January 2018 using the query *essential tremor AND surgery* produced 839 abstracts. 379 papers were selected for review of the methods, efficacy, safety and expense of stereotactic deep brain stimulation (DBS), stereotactic radiosurgery (SRS), focused ultrasound (FUS) ablation, and radiofrequency ablation of the cerebellothalamocortical pathway.

Expert commentary: DBS and SRS, FUS and radiofrequency ablations are capable of reducing upper extremity tremor by more than 80% and are far more effective than any available drug. The main research questions at this time are: 1) the relative safety, efficacy, and expense of DBS, SRS, and FUS performed unilaterally and bilaterally; 2) the relative safety and efficacy of thalamic versus subthalamic targeting; 3) the relative safety and efficacy of atlas-based versus direct imaging tractography-based anatomical targeting; and 4) the need for intraoperative microelectrode recordings and macroelectrode stimulation in awake patients to identify the optimum anatomical target. Randomized controlled trials are needed.

ARTICLE HISTORY
Received 15 December 2017
Accepted 22 February 2018

KEYWORDS
Essential tremor; functional neurosurgery; deep brain stimulation; focused ultrasound; stereotactic radiosurgery; thalamotomy

1. Introduction

Essential tremor (ET) is a syndrome of action tremor in the upper limbs and frequently in the head and voice [1]. The lower limbs and torso may also be affected. ET is the most common form of pathologic tremor. It may manifest in childhood, but its incidence and prevalence increase with age, affecting an estimated 4.5% of people over age 65 [2].

The etiologies of ET are unknown [3]. Many patients have a family history of tremor consistent with a Mendelian dominant pattern of inheritance. However, no disease-causing or risk-conferring genes have been consistently found in large families and patient cohorts. Postmortem findings have also been inconsistent. No abnormalities have been identified in some postmortem studies, but cerebellar Purkinje cell loss and associated abnormalities have been found in others [3].

The cerebellum is believed to play a pivotal role in ET pathophysiology because lesions and high-frequency electrical stimulation in the cerebellar receiving nucleus of the thalamus, ventralis intermedius (Vim; a.k.a., ventralis lateralis posterior), suppress ET [4,5]. Furthermore, many neuroimaging and electrophysiologic studies have demonstrated neuronal activation and oscillation in the corticobulbocerebellothalamocortical loop [6–8]. This loop appears to be involved in virtually all forms of pathologic tremor [5], which is fortuitous given that ET and other tremor disorders are often mistaken for each other. Strokes in locations throughout the corticobulbocerebellothalamocortical loop have been observed to suppress ET [4]. Surgical ablation of Vim or the posterior subthalamic area (PSA) immediately below Vim is particularly effective in suppressing ET by disrupting oscillation in the cerebellothalamocortical pathway [9–12]. High-frequency deep brain stimulation (DBS) in Vim or PSA disrupts tremorogenic oscillation in these loops primarily by stimulating nerve axons within a few millimeters of the DBS electrode [13]. However, the origin of tremorogenic oscillation within this loop is unknown for ET, and it is unknown to what extent the components of the corticobulbocerebellothalamocortical loop are capable of suppressing or causing tremorogenic oscillation. The excitatory reciprocal thalamocortical loop is possibly capable of amplifying oscillation of any origin [3,14,15].

Here we review the surgical treatment of ET with emphasis on topics that were not emphasized in previous evidence-based reviews [9–12]. The immediate or short-term (≤12 months) efficacy of ablative surgery and deep brain stimulation (DBS) is undeniable, despite the lack of randomized controlled trials [16], and published short-term studies are briefly reviewed here with emphasis on treatment magnitude and adverse effects. Greater attention is devoted to published long-term studies, the loss of efficacy over time, patient selection, optimum anatomical target location, and pressing questions to be answered in future clinical trials.

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2. Methods

A search of PubMed on 1 October 2017 and again on 18 January 2018 using the query *essential tremor AND surgery* produced 839 abstracts, from which 307 papers were selected for review. The reference lists in these papers were also searched for relevant articles, producing an additional 72 papers. We excluded papers that reported results for multiple disorders (e.g. Parkinson disease, ET and dystonia) unless we could confidently extract efficacy data for ET. In some instances, efficacy data for ET could be extracted, but adverse events could not. General reviews of perioperative complications were included. We excluded papers with only qualitative reports of efficacy (e.g. 'mild or moderate residual tremor', 'almost free of tremor').

We found that nearly all authors used clinical rating scales to assess efficacy, and improvement was usually expressed as a percentage of the baseline tremor rating. The Fahn–Tolosa–Marín tremor rating scale (FTM) and the Essential Tremor Rating Assessment Scale (TETRAS) were used most commonly [17,18]. These scales consist of items that assess tremor with ordinal ratings of 0 to 4. Expressing improvement as a percentage of these ratings is misleading and incorrect because such rating scales are not linear measures of tremor amplitude [19]. A reduction in tremor from grade 4 to grade 2 was commonly expressed as a 50% reduction, and the same percentage reduction was also computed for a change in tremor from grade 2 to grade 1. However, it has been shown that tremor amplitude *T*, measured with a motion transducer, is logarithmically related to tremor ratings *R*, according to Equation 1, with the subscripts 1 and 2 designating the initial and final values (Figure 1) [19].

$$log_{10}T = \propto R + \beta \quad (1)$$

$$\frac{T_2 - T_1}{T_1} = 10^{\propto(R_2 - R_1)} - 1 \quad (2)$$

Studies have shown that the coefficient α is 0.4 to 0.6 for upper extremity tremor and head tremor, and β is typically −1 to −3 [19–22]. The fractional change in tremor amplitude for a given change in rating is derived from Equation 1 and is given in Equation 2. The percentage change in tremor amplitude is the result of Equation 2 times 100. Note that the percentage change in tremor amplitude is a function of the change in tremor rating, not the percentage change in tremor rating. A two-point reduction in tremor is much greater than a one point reduction, regardless of the baseline or initial rating.

Scales with a maximum score or rating greater than 4 are still logarithmically related to tremor amplitude [21]. In general, the value of α for a rating scale with maximum score *S* (α_S) is 4/*S* times α for a 0 to 4 scale (α_4), as given in Equation 3 [10].

$$\propto_S = \propto_4 \left(\frac{4}{S}\right) \quad (3)$$

In this review, we computed α_S for scales used in various studies by assuming $\alpha_4 = 0.4$, and with this value in Equation 2, we estimated the percentage change in tremor amplitude. This value of α_4 is at the lower range of values reported, so estimates of efficacy in this review are conservative. A previous review using this methodology assumed $\alpha_4 = 0.5$ [10]. For

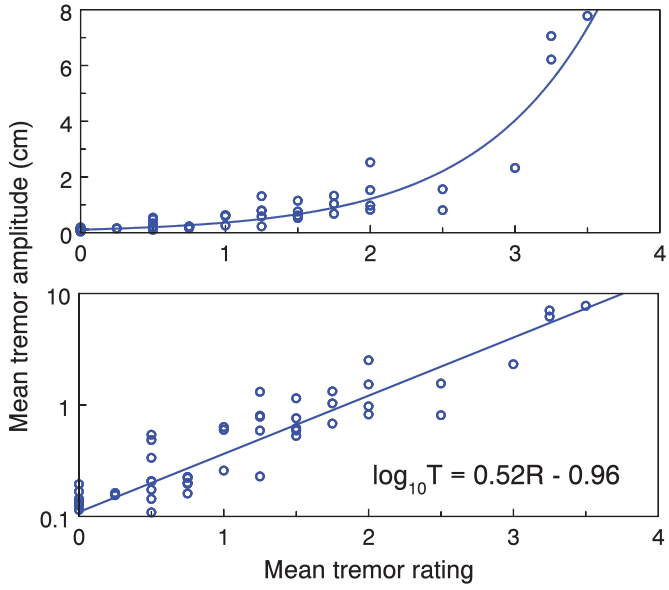

Figure 1. Nineteen patients with essential tremor drew Archimedes spirals on a digitizing tablet twice with each hand on two separate days (*N* = 38 assessments). Maximum tremor amplitude in any 3-second time interval in each drawing was computed with spectral analysis, and tremor was rated 0–4 using the Fahn–Tolosa–Marín rating scale. The mean tremor amplitude (*T*) in the four drawings is plotted in the top graph versus the mean tremor rating (*R*), illustrating the exponential relationship between *T* and *R*. In the lower graph, the linear relationship between $\log_{10}T$ and *R* is shown. The coefficient of variation of the linear regression was 0.85.

$\alpha_4 = 0.4$ in Equation 2, a change in rating from 4 to 2 is an 84% reduction in tremor, and a change in rating from 2 to 1 is a 60% reduction. For $\alpha_4 = 0.5$ in Equation 2, a change in rating from 4 to 2 is a 90% reduction in tremor, and a change in rating from 2 to 1 is a 68% reduction. Note that the estimated percentage change in tremor will never be 100%, consistent with the reality that tremor is never completely abolished, for physiologic tremor always remains even when the pathologic tremor is abolished.

Many studies also assessed the impact of surgery on activities of daily living (ADL), and some studies assessed quality of life. ADL scales correlate strongly with tremor amplitude ratings (i.e. performance scales) [23], and ADLs and especially quality of life assessments are influenced by psychosocial factors (e.g. depression) that are not directly related to tremor amplitude [24]. Therefore, we do not report the details of ADL and quality of life assessments, rather we simply report when these assessments were done and if the results were statistically significant.

3. Results

3.1. Patient selection

Epidemiologic studies have shown that most ET patients have relatively mild tremor and have not seen a physician for their condition [25]. Patients presenting for surgery usually are severely affected such that their tremor interferes with most fine motor tasks. Head tremor may be a significant cosmetic concern. Voice tremor may impair communication. ET typically progresses slowly over decades [26,27], but some patients

present with a short history of less than 10 years and unusually rapid progression. Rapid progression should alert the clinician to some other tremor disorder or comorbidity. There is a growing concern that many patients selected for surgery do not have ET but instead have dystonic tremor, focal dystonia associated with tremor, or some form of tremor-predominant ataxia [28]. The presence of unrecognized dystonia or ataxia could impact a patient's quality of life after an otherwise successful surgery and could also predispose the patient to adverse effects, such as dysarthria and gait disturbances.

Patient selection for surgery is based on the principle of selecting patients who possess factors favoring a high benefit/risk ratio. There are no evidence-based guidelines for selecting patients. Surgical candidates are generally patients who have failed best medical therapy: propranolol, primidone, and topiramate. These medications are frequently inadequate, even for patients with mild to moderate tremor [10]. Propranolol and primidone are most effective but produce an average reduction in postural tremor of only 50 to 60% [5], and the reduction in kinetic tremor is usually less. An occasional patient will exhibit a more dramatic response, but this is rarely long-lasting [5]. No currently available drug is as effective as available surgical treatments [5].

Surgical complications of thalamic DBS and ablative surgery include intracranial hemorrhage, infarction, infection, and encephalopathy. Dysarthria, sensory disturbances, and gait disturbances are the most common neurological symptoms experienced following surgery. Some centers have multidisciplinary teams that screen for patients who may be at increased risk for adverse effects [29]. Major and minor concerns may be identified, but the ultimate decision to accept or reject a patient is usually somewhat subjective. Prospective randomized studies are needed to compare the multidisciplinary team approach to the judgment of an experienced neurologist and neurosurgeon.

Careful patient selection could conceivably reduce the incidence of adverse outcomes, but it could also preclude surgery for high-risk patients that might benefit. Ideally, patients should decide after being informed of the potential risks and benefits. Comorbid depression and anxiety are not uncommon in ET, and quality of life is strongly influenced by psychosocial factors [25]. Consequently, psychosocial factors may influence a patient's level of satisfaction after surgery and may influence a patient's decision to seek any form of treatment [25].

Nearly all surgical teams screen patients for dementia and consider dementia a relative contraindication for surgery. However, evidence-based guidelines are not available. Some surgical teams merely use clinical judgement and bedside examination (e.g. Mini Mental State Examination [30]) to select candidates for surgery [31]. Other surgical teams employ a neuropsychologist and more extensive neuropsychological evaluation [29]. Many teams do not use strict cutoffs for measures of cognitive function [32]. Others use a score ≤130 on the Mattis Dementia Rating Scale to exclude patients with cognitive impairment [33,34]. A Mini Mental State Score <24 has also been used [35], but published normative data support a cutoff score of 25 for older people with >10 years of education [36,37]. This cutoff score should be adjusted upward for younger age groups [36,37]. In patients screened for dementia, there appears to be little or no risk of cognitive decline after DBS or thalamotomy [38–41]. One study found that post-operative cognitive decline was associated with higher pulse width in DBS but not with age or baseline cognitive function [41]. Mild group-wise loss of verbal fluency has been found in some studies [42], particularly after surgery on the left [38], but reduced verbal fluency is subclinical or absent in most patients [39,40,43]. The risk of surgery in patients with baseline cognitive impairment is suspected to be greater but has not been studied.

General health (i.e. comorbidities) rather than age is used in patient screening because age per se is not a good predictor of patient outcome [33,44]. Patients as old as 88 have undergone successful DBS surgery [45], and patients as old as 89 and 93 have undergone focused ultrasound (FUS) [46] and stereotactic radiosurgery (SRS; e.g. Gamma Knife radiosurgery) ablations [47]. A large claims-based analysis examined age as a potential predictive factor for surgical complications and found no relationship [44]. Pronounced cerebral atrophy or signs of severe cerebral microangiopathy on MRI have been used as exclusion criteria [48], but we found no data to support clear guidelines.

SRS has been proposed as an alternative for patients with relative contraindications to DBS. Common reasons for offering SRS are advanced age, medical comorbidities, anticoagulation therapy, and patient refusal of DBS [49], with advanced age and medical comorbidities being most common [50]. Patients with MRI-incompatible cardiac pacemakers cannot undergo MRI, which precludes the possibility of FUS ablation therapy and the possibility of using MRI for anatomical target location.

It is curious that 63% of patients in the papers we reviewed were men, but only about one third of published epidemiologic studies found a male preponderance for ET [2]. Therefore, it is unclear whether the male preference in surgical studies is due to selection bias, a difference in progression/severity in men versus women, or a relative aversion of women to these surgical procedures.

3.2. Short-term (≤12 months) efficacy

There are no randomized controlled trials of DBS for ET, and we found only one randomized controlled trial of thalamotomy [46]. Consequently, surgical treatments for ET are reported as 'possibly effective' in evidence-based reviews [9–11]. This terminology reflects the strength of published data, not the degree of efficacy, because these procedures are the only available treatments that are capable of abolishing severe tremor.

3.2.1. Radiofrequency ablation

Using Equations 1–3, we estimated the actual change in tremor amplitude produced by radiofrequency thalamotomy (Table 1). We found that most studies were published before the advent of validated tremor rating scales, so the computation of treatment effect, using our methods, was possible for only three studies [35,51,52]. Upper extremity postural and kinetic tremor decreased an average of

Table 1. Short-term (≤12 months) efficacy of unilateral and bilateral DBS and ablative therapies for essential tremor.

Study	Study design/target	Number of patients/ treatment	Mean age ±SD (range) at surgery	Mean baseline → followup tremor scores (maximum total score)[a]	Percentage reduction in tremor amplitude
Radiofrequency ablation					
Goldman [51]	UCS/Vim	7 unilateral 1 bilateral	46.6 (18–69)	baseline → 1–50 months (3 patients > 8 months) UE tremor (max 4): 2.25 → 0.25[b]	84
Zirh [52]	Blinded writing/drawing exams/Vim	18 unilateral 3 bilateral	60.6 ± 15.7	Baseline → 3 → 12 months UE postural tremor (max 4): 3.0 → 0.7 → 0.9 UE kinetic tremor (max 4): 3.5 → 0.6 → 0.6 Writing/drawing (max 12): 6.3 → 2.8 → 2.9	88, 86 93, 93 66, 65
Stereotactic radiosurgery					
Young [47]	UCS/Vim	119 unilateral 42 bilateral	72 ± 11 (18–93)	Baseline → 6 → 12 months Writing (max 4): 3.1 → 1.26 → 1.04 Drawing (max 4): 3.3 → 1.72 → 1.51	82, 85 77, 81
Focused ultrasound ablation					
Chang [54]	UCS/Vim	11 unilateral (3 could not be lesioned)	64.6 ± 7.4 (53–78)	Baseline → 6 months UE rest/postural/kinetic (max 12): 5.1 → 1.4 Writing/drawing (max 20): 13 → 2.6	68 85
Elias [53]	UCS/Vim	15 unilateral	66.6 ± 8.0	Baseline → 3 → 12 months UE rest/postural/kinetic + writing/drawing/ pouring (max 32): 20.4 → 4.3 → 5.2	84, 83
Elias [46]	RCT/Vim	52 unilateral 20 sham	71.0 ± 8.3 (47–89)	Baseline → 3 → 12 months UE rest/postural/kinetic + writing/drawing/ pouring (max 32): 18.1 → 9.6 → 10.9	62, 56
Gallay [56]	UCS/PSA	18 unilateral 3 bilateral	69.1 ± 9.2	Baseline → 3 → 12 months Drawing/pouring (max 16): 12.4 → 3.7 → 3.7	87, 87
Lipsman [55]	UCS/Vim	4 unilateral	70.8 (58–77)	Baseline → 3 months UE rest/postural/kinetic (max 12): 7.25 → 1.25	84
Schreglmann [57]	Blinded video exams/PSA	6 unilateral	70.7 ± 8.5	Baseline → 6 months UE rest/postural/kinetic + drawing/pouring (max 28): 14.3 → 2.5	79
Deep brain stimulation					
Blomstedt [59]	UCS/Vim vs PSA	Vim 31 unilateral 3 bilateral PSA 31 unilateral 3 bilateral	61.5 ± 14.8 58.2 ± 16.5	Baseline → 12 months Vim UE rest/postural/kinetic (max 12): 6.4 → 1.2 Drawing/pouring (max 16): 11.6 → 4.2 PSA UE rest/postural/kinetic (max 12): 6.2 → 0.2 Drawing/pouring (max 16): 9.5 → 1.5	80 82 84 84
Chang [60]	UCS/Vim + PSA	5 bilateral	62.6 (54–67)	Baseline → 12 months UE postural (max 4): 1.9 → 0.1[c] UE kinetic (max 4): 2.6 → 0.6[c]	81 84
Fenoy [129]	UCS/CTT	2 unilateral 18 bilateral	66.8 (41–84)	Baseline → <3 months UE action (max 4): 2.6 → 0.8[c]	81
Fytagoridis [61]	UCS/cZi	42 unilateral 8 bilateral	63.5 ± 13.1	Baseline → 12 months UE rest/postural/kinetic (max 12): 6 → 0.3 Drawing/pouring (max 16): 10.5 → 2	83 86
Koller [62]	UCS/Vim	29 unilateral	66.8 ± 11.5	Baseline → 12 months Writing (max 4): 3.0 → 1.3 Drawing (max 4): 3.1 → 1.6 Pouring (max 4): 3.0 → 1.1	79 75 83

(*Continued*)

Table 1. (Continued).

Study	Study design/target	Number of patients/ treatment	Mean age ±SD (range) at surgery	Mean baseline → followup tremor scores (maximum total score)[a]	Percentage reduction in tremor amplitude
Kumar [69]	UCS/Vim	4 unilateral 5 bilateral	69 ± 10 (50–80)	Baseline → 14.9 ± 8.1 months UE postural (max 4): 2.6 → 0.4 UE kinetic (max 4): 3.5 → 0.3 Writing/drawing/pouring (max 32): 22.9 → 10.1	87 95 77
Limousin [63]	UCS/Vim	28 unilateral 9 bilateral	63.1 ± 12.7	Baseline → 3 → 12 months UE rest/postural/kinetic (max 12): 7.27 → 1.42 → 1.42	83, 83
Ondo [64]	Blinded exams at 3 months/Vim	14 unilateral	72.3 ± 4.8	Baseline → 3 months UE rest/postural/kinetic (max 12): 7.3 → 2.8[d]	75
Ondo [30]	Blinded exams at 3 months/Vim	13 bilateral	71.5 ± 4.9	Baseline → 3 months UE rest/postural/kinetic (max 12): 6.7 → 1.3[d]	81
Pahwa [65]	Blinded exams at 3 months/Vim	9 bilateral	73.8 (63–79)	Blinded 3 month scores with stimulation off → on UE action side 1 (max 8): 6 → 2 UE action side 2 (max 8): 5.2 → 2 Unblinded scores at baseline → 6 → 12 months UE action side 1 (max 8): 5.8 → 1.2 → 1.7 UE action side 2 (max 8): 6.1 → 1.8 → 1.6 Drawings side 1 (max 12): 10.7 → 4 → 3.9 Drawings side 2 (max 12): 9.7 → 6.7 → 5.4 Pouring side 1 (max 4): 3.2 → 1.4 → 1.8 Pouring side 2 (max 4): 3.6 → 1.8 → 2	84 77 88, 85 86, 87 87, 88 60, 73 81, 72 81, 77
Plaha [68]	UCS/PSA	4 bilateral	66.8 ± 8.5	Baseline → 12 months UE action (max 4): 3.2 → 0.5 Writing/drawing/pouring (max 36): 24.3 → 8	92 81
Sandvik [66]	UCS/cZi	14 unilateral 2 bilateral	60.9 ± 14.7	Baseline → 12 months UE rest/postural/kinetic (max 12): 6.3 → 0.4 Drawing/pouring (max 16): 9.9 → 2.1	84 83
Wharen [70]	Blinded video exams at 6 months/Vim	80 unilateral 47 bilateral	64.6 ± 9.6	Baseline → 6 months (blinded exams in 68 patients) UE action (max 4): 2.49 → 0.87 Baseline → 12 months (unblinded exams in 112 patients) UE action (max 4): 3.11 → 0.62 (unblinded exams)	76 90
Deep brain stimulation versus focused ultrasound					
Huss [67]	UCS/Vim	DBS 57 bilateral 13 unilateral FUS 15 unilateral	63.5 71.7 67.2	Baseline → 12 months UE rest/postural/kinetic + writing/drawing/pouring (max 32) DBS bilateral: 20.4 → 5.2 DBS unilateral: 18.5 → 5.6 FUS unilateral: 20.4 → 5.7	83 77 82
Deep brain stimulation versus radiofrequency ablation					
Schuurman [35]	Randomized treatment. Blinded video exams/Vim	7 DBS 6 thalamotomy	62 ± 17.0 64 ± 7.6	Baseline → 6 months UE action (max 4) with DBS: 3.57 → 0[b] UE action (max 4) with thalamotomy: 3.5 → 0[b]	96 96

[a]Fahn–Tolosa–Marín (FTM) ratings unless otherwise noted
[b]ad hoc scale
[c]The Essential Tremor Rating Assessment Scale (TETRAS)
[d]Unified Tremor Rating Assessment
CTT:cerebellothalamic tract; cZi: caudal zona incerta; DBS: deep brain stimulation; PSA: posterior subthalamic area; RCT: randomized controlled trial; UCS: uncontrolled study; UE: upper extremity; Vim: ventralis intermedius

84–96%, and writing/drawing tremor decreased 65% (Table 1). ADL scores improved in all three studies.

3.2.2. Focused ultrasound ablation

A randomized double-blind sham-controlled trial of MRI-guided focused ultrasound (FUS) Vim thalamotomy revealed a mean 62% improvement in contralateral upper extremity tremor amplitude at 3 months (Table 1) [46]. Physician-blinded assessments of patient videos at 12 months revealed a mean 56% improvement, and quality of life also improved. Three earlier unblinded pilot studies [53–55] revealed even greater improvement although successful ablation of Vim was not always possible [54].

In a pilot study of FUS ablation of the cerebellothalamic tract in the PSA, 21 patients exhibited a mean 87% improvement in drawing/pouring tremor [56]. Three patients underwent successful bilateral surgery with one year between procedures. In a second pilot study with blinded video exams, 6 patients experienced a 79% reduction in upper extremity tremor and significant improvement in quality of life [57].

3.2.3. Stereotactic radiosurgery

SRS was recently reviewed by Higuchi and coworkers [58]. In one uncontrolled study of 161 patients, the average percentage reductions in writing tremor at 6 and 12 months were 82 and 85%, and those for drawing tremor were 77 and 81% [47]. ADL and quality of life were not assessed.

3.2.4. Deep brain stimulation

We found 13 studies [30,59–70] with sufficient data to allow us to compute the percentage reduction in tremor amplitude. All were unblinded uncontrolled studies except for blinded 3-month videotaped exams in 3 studies [30,64,65]. The anatomical target in the 13 studies was Vim [30,62–65,67,69], PSA [61,66,68], or both [59,60]. The average percentage improvement in upper extremity tremor at 12 months ranged from 73–96% (Table 1). ADL and quality of life also improved [66,67,69–71].

3.2.5. Comparative short-term studies

Huss and coworkers compared bilateral (N = 57) and unilateral (N = 13) Vim DBS to unilateral FUS thalamotomy (N = 15) in an uncontrolled study, and the improvements in contralateral upper extremity tremor, ADL, and quality of life were not significantly different for the two methods [67]. Schuurman and coworkers compared radiofrequency thalamotomy (N = 6) to Vim DBS (N = 7) in a study of randomly allocated patients evaluated by blinded video assessments, and both groups had comparable improvement in upper extremity tremor and ADL at 6 months followup [35]. Tasker also found that radiofrequency thalamotomy and Vim DBS were comparable in efficacy [72].

3.3. Long-term (>12 months) studies

3.3.1. Radiofrequency ablation

We found no long-term studies of radiofrequency thalamotomy.

3.3.2. Stereotactic radiosurgery

Enthusiasm for SRS has been limited because the correct target and optimum lesioning cannot be confirmed during the procedure. The target is identified using atlas-based AC-PC coordinates, and symptomatic benefit and adverse effects take 1–4 months or more to develop. Therefore, long-term followup is necessary in studies of this procedure. We found 3 published studies in which many patients continued to benefit beyond 12 months [49,73,74], but patient dropout and variability in the duration of followup were so great in all three studies that efficacy at specific time intervals was impossible to estimate. The estimates in Table 2 are for highly variable followup intervals. A small study with blinded video evaluations found only modest (<50%) reductions in upper extremity tremor (Table 2) [73].

3.3.3. Focused ultrasound ablation

Sixty seven of 76 patients in a randomized controlled trial of FUS thalamotomy [46] completed a 2-year open-label followup with blinded video exams [75]. Three of the nine dropouts underwent DBS, and one had failed therapy due to hyperostosis frontalis interna. The remaining five patients dropped out due to cancer (N = 2) or unspecified reasons (N = 3). Dropouts were included in the analyses, which revealed >70% reductions in upper extremity postural and kinetic tremors (Table 2) and significant improvement in ADL scores.

3.3.4. Deep brain stimulation

We found 13 papers with long-term followup data for Vim or PSA DBS (Table 2) [45,76–88]. Patient dropout and variability in the duration of followup were so great in all 13 studies that accurate efficacies at specific time intervals were not possible to estimate. The estimates in Table 2 are for highly variable followup intervals. Nevertheless, it is clear that most patients continue to experience more than 70% reduction in upper extremity tremor for several years or more.

3.4. Midline tremor

Papers with data pertaining to midline tremor (head/neck, face, voice, tongue, and trunk) are summarized in Table 3. Bilateral surgery seems to have a greater effect on voice tremor [30,89–92] and head tremor [30,63,91,92], but the numbers of patients are small, and significant results are not always seen [76,93]. More medial placement of the DBS electrode or ablation in Vim may result in greater suppression of voice and head tremor [94], but this may also result in less suppression of extremity tremor, which is usually most disabling. In one study, a more vertical trajectory in the sagittal plane (relative to AC-PC line) correlated with greater improvement in head tremor [93]. DBS may be more effective than FUS thalamotomy in controlling midline tremor [67]. Patients with predominantly vocal or head tremor with mild or no upper limb tremor most likely have vocal or cervical tremulous dystonia, not ET [28]. These differences in diagnosis could influence anatomical target selection [95].

Table 2. Long-term (>12 months) efficacy of DBS and ablative therapies for essential tremor.

Study	Study design/ target	Number of patients/ treatment	Mean age ±SD (range) at surgery	Mean baseline → followup tremor scores (maximum total score)[a]	Percentage reduction in tremor amplitude
Stereotactic radiosurgery					
Kondziolka [49]	UCS/Vim	26 unilateral	77 (52–92)	Baseline → 4–96 months (mean 36) UE action (max 4): 3.7 → 1.7 Writing (max 4): 2.8 → 1.7 3 patients did not improve.	84 64
Lim [73]	Blinded video exams/Vim	11 unilateral	75.8 ± 6.0 (64–83)	Baseline → 7–30 months (mean 19.2) Writing (max 4): 3 → 2.3 Drawings (max 12): 9.4 → 8.5 Pouring (max 4): 3.4 → 3.3	48 24 9
Niranjan [74]	UCS/Vim	73 unilateral	77 (43–92)	Baseline → 6–152 months (mean 28) Writing (max 4): 2.85 → 0.96 Water drinking (max 4): 3.11 → 1.04 Drawing (max 4): 2.96 → 0.79 11 patients did not improve.	82 85 86
Focused ultrasound ablation					
Chang [75]	Blinded video exams/Vim	76 unilateral 9 dropouts at 24 months	71.0 ± 8.3 (47–89)	Baseline → 6 → 12 → 24 months UE rest/postural/kinetic + writing/drawing/pouring (max 32): 19.8 → 8.6 → 8.9 → 8.8 UE postural (max 4): 2.9 → 0.8 – > 0.8 → 0.9 UE kinetic (max 4): 2.9 → 1.2 → 1.2 → 1.4	72, 71, 72 86, 86, 84 79, 79, 75
Deep brain stimulation					
Baizabal-Carvallo [76]	Blinded video exams/Vim	7 bilateral 6 unilateral	68 (37–78)	Baseline → 114–164 months UE rest/postural/kinetic (max 12): 8.7 → 4 UE postural (max 4): 2.85 → 1.15 UE kinetic (max 4): 2.77 → 1.62 Drawing/pouring (max 16): 13.75 → 9.45	76 79 65 63
Blomstedt [77]	UCS/Vim	19 unilateral	68 (48–80)	Baseline → 6–26 → 66–102 months UE postural (max 4): 2.5 → 0.2 → 0.5 UE kinetic (max 4): 3.5 → 1.1 → 2.0 Drawing/pouring (max 16): 12.7 → 4.1 → 8.2	88, 84 89, 75 86, 65
Cury [78]	UCS/Vim	35 bilateral 3 unilateral	63.6	12 month scores with stimulation off → on FTM Part A (max 80): 22.2 → 7.5 >120 month scores with stimulation off → on FTM Part A (max 80): 28.3 → 14.7	49 47
Fytagoridis [79]	UCS/cZi	16 unilateral 2 bilateral	62.6 (34–62)	Baseline → 34–62 months (mean 48.5) UE postural (max 4): 2.4 → 0.1 UE kinetic (max 4): 3.4 → 0.5 Drawing/pouring (max 16): 9.1 → 2.0	88 93 81
Koller [80]	UCS/Vim	25 unilateral	70.7 ± 10.3 (42–87)	Baseline → 24 months UE rest/postural/kinetic (max 12): 6.5 → 1.4 7 patients in the original cohort of 49 patients had explanted hardware.	79
Murata [82]	UCS/PSA	8 unilateral	64.6 ± 8.1 (50–72)	Baseline → 8–42 months (median 22) Total tremor score (max 41): 20.5 → 4.25[b]	77
Nazzaro [45]	UCS/Vim	78 unilateral	71.9 ± 9.1 (42–88)	UE rest/postural/kinetic (max 12): Baseline → followup 12 months (78 patients): 6 → 0.9 24–84 months (42 patients): 5.9 → 1.7 84–144 months (22 patients): 5.0 → 1.9	79 72 61
Pahwa [83]	UCS/Vim	7 bilateral 16 unilateral	70.6 ± 5.3 (57–78)	FTM Part A (max 84) baseline → 60 months Bilateral DBS: 29 → 6.4 Unilateral DBS: 21.5 → 11.7 UE action (max 4): 3.2 → 0.8	63 35 89
Papavassiliou [84]	UCS/Vim	16 bilateral 21 unilateral	66.2 ± 13.6 (31–85)	Baseline → 3–60 months (mean 26) UE rest/postural/kinetic + writing/drawing/pouring (max 28): 19.3 → 9.1	74
Plaha [85]	UCS/cZi	15 bilateral	65.4 ± 7.9	Baseline → 12–84 months (mean 31.7) Writing/drawing/pouring (max 36): 24.7 → 9.9	78
Putzke [86]	UCS/Vim	23 bilateral 29 unilateral	72.3 ± 8.4	Baseline → 3 → 12 → 36 months UE rest/postural/kinetic (max 12): 6.9 → 1.2 → 0.8 → 0.9	83, 85, 84
Rehncrona [87]	Blinded exams/ Vim	2 bilateral 16 unilateral	65.5 ± 10.5	Baseline → 24 (18 patients) → 72 months (13 patients) UE postural (max 4): 3 → 1 → 1 UE kinetic (max 4): 3 → 1 → 1.5 Drawing/pouring (max 16): 14 → 4 → 4	84, 84 84, 75 90, 90
Sydow [88]	UCS/Vim	12 unilateral 7 bilateral	65 (40–78)	Baseline → 12 → 66–92 months (mean 78) UE postural (max 4): 3 → 0.5 → 0.9 UE kinetic (max 4): 3.4 → 1 → 1.7	90, 86 89, 79

[a] The Fahn–Tolosa–Marín scale (FTM) was used in all studies except Murata et al. [82].
[b] Ad hoc modification of the FTM
cZi: caudal zona incerta; DBS: deep brain stimulation; PSA: posterior subthalamic area; RCT: randomized controlled trial; UCS: uncontrolled study; UE: upper extremity; Vim: ventralis intermedius

Table 3. Efficacy of DBS for midline tremors.

Study	Study design/target	Number of patients/ treatment	Mean age ±SD (range) at surgery	Mean baseline → followup tremor scores (maximum total score)[a]	Percentage reduction in tremor amplitude
Berk and Honey [90]	Blinded video exams/Vim	2 bilateral	43, 41	Baseline → 9 months	96
				Head (max 4): 3.4 → 0[b]	75
				Voice (max 4): 1.5 → 0	
Blomstedt [59]	UCS/Vim vs PSA	Vim	61.5 ± 14.8	Baseline → 12 months	45
		31 unilateral	58.2 ± 16.5	Vim	42
		3 bilateral		Head (max 8): 1.7 → 0.4	21
		PSA		Voice (max 4): 0.9 → 0.3	31
		31 unilateral		PSA	
		3 bilateral		Head (max 8): 0.6 → 0.1	
				Voice (max 4): 0.5 → 0.1	
Baizabal-Carvallo [76]	Blinded video rating/Vim	6 unilateral	68	Baseline → 114–164 months	27
		7 bilateral	(37–78)	Head (max 8): 1.38 → 0.69	–7
				Voice (max 4): 2.08 → 2.15	
Fenoy [129]	UCS/CTT	2 unilateral	66.8	Baseline → <3 months	75
		18 bilateral	(41–84)	Head (max 4): 2.3 → 0.8[c]	
Hägglund [89]	Blinded recordings/cZi	11 unilateral	68.1 ± 14.3	Baseline → 5–103 months (mean 54.2)	51
		2 bilateral	(31.8–86.8)	Voice (max 4): 1.42 → 0.65[b]	
Koller [96]	UCS/Vim	38 unilateral	71.8 ± 9.8	Baseline → 3 → 6 → 12 months	47, 44, 50
				Head (max 8): 2.75 → 1.36 → 1.51 → 1.26	
Limousin [63]	UCS/Vim	28 unilateral	63.1 ± 12.7	Baseline → 3 → 12 months	15, 7
		9 bilateral		Unilateral	13, 13
				Head (max 8): 1.00 → 0.64 → 0.85	56, 58
				Voice (max 4): 0.46 → 0.31 → 0.31	51, 33
				Bilateral	
				Head (max 8): 2.22 → 0.44 → 0.33	
				Voice (max 4): 1.11 → 0.33 → 0.67	
Moscovich [93]	UCS/Vim	23 unilateral	73 ± 13.4	Baseline → 12 months	87
		6 bilateral		Head (max 8): 2.62 → 0.42	
Obwegeser [91]	UCS/Vim	14 unilateral	73 ± 5.2	Baseline → 11–12 months	52
		13 bilateral		Unilateral	37
				Head (max 4): 2.1 → 1.3	75
				Voice (max 4): 1.8 → 1.3	70
				Tongue (max 4): 1.6 → 0.1	75
				Face (max 4): 2.0 → 0.7	84
				Trunk (max 4): 2.0 → 0.5	75
				Bilateral	77
				Head (max 4): 2.1 → 0.1	84
				Voice (max 4): 1.8 → 0.3	84
				Tongue (max 4): 1.6 → 0	
				Face (max 4): 2.0 → 0	
				Trunk (max 4): 2.0 → 0	
Ondo [64]	Blinded exams/Vim	14 unilateral	72.3 ± 4.8	Baseline → 3 months	64
				Head (max 4): 2.1 → 1[d]	9
				Voice (max 4): 2 → 1.9[d]	
Ondo [30]	Blinded exams/Vim	13 bilateral	71.5 ± 4.9	Baseline → 3 months	52
				Head (max 4): 1.8 → 1[d]	48
				Voice (max 4): 1.2 → 0.5[d]	
Plaha [85]	UCS/cZi	15 bilateral	65.4 ± 7.9	Baseline → 12–84 months (mean 31.7)	56
				Head (max 8): 1.9 → 0.13	17
				Voice (max 4): 0.6 → 0.4	25
				Face (max 8): 0.7 → 0.07	24
				Trunk (max 8): 0.6 → 0	

(*Continued*)

Table 3. (Continued).

Study	Study design/target	Number of patients/ treatment	Mean age ±SD (range) at surgery	Mean baseline → followup tremor scores (maximum total score)[a]	Percentage reduction in tremor amplitude
Putzke [92]	UCS/Vim	22 bilateral	70.3 ± 9.0	Baseline → ≥3 months	42
				Unilateral stimulation:	42
				Head (max 8): 2.1 → 0.9	24
				Voice (max 4): 1.7 → 1.1	42
				Tongue (max 8): 0.9 → 0.3	17
				Face (max 4): 0.7 → 0.1	58
				Trunk (max 8): 0.4 → 0	72
				Bilateral stimulation	34
				Head (max 8): 2.1 → 0.2	48
				Voice (max 4): 1.7 → 0.3	17
				Tongue (max 8): 0.9 → 0	
				Face (max 4): 0.7 → 0	
				Trunk (max 8): 0.4 → 0	
Sydow [88]	UCS/Vim	12 unilateral 7 bilateral	65 (40–78)	Baseline → 12 → 66–92 months (mean 78)	9, 21
				Unilateral:	24, 9
				Head (max 8): 1.1 → 0.9 → 0.6	54, 54
				Voice (max 4): 0.4 → 0.1 → 0.3	21, 24
				Bilateral:	
				Head (max 8): 2 → 0.3 → 0.3	
				Voice (max 4): 1 → 0.5 → 0.4	

[a] Fahn–Tolosa–Marín (FTM) ratings unless otherwise noted
[b] Ad hoc rating
[c] The Essential Tremor Rating Assessment Scale (TETRAS)
[d] Unified Tremor Rating Assessment
CTT: cerebellothalamic tract; cZi: caudal zona incerta; DBS: deep brain stimulation; PSA: posterior subthalamic area; RCT: randomized controlled trial; UCS: uncontrolled study; Vim: ventralis intermedius

3.5. Adverse effects of radiofrequency ablation

Postoperative dysarthria, hemiataxia, gait ataxia and contralateral sensory disturbances are common, and one or more of these deficits persist in 20–30% of patients and are even more common after bilateral thalamotomy [12,51,52,72,97,98]. A recent review of published reports as of September 2014 produced an estimated 4.5% (95% CI: 2.3–8.7) risk of speech disturbance after unilateral surgery and 13.9% (95% CI: 1–95) after bilateral surgery in patients with ET [99]. Loss of efficacy is also common after radiofrequency thalamotomy. Tasker reported that 23% of patients required additional lesioning to control tremor [72].

3.6. Adverse effects of focused ultrasound ablation

In a randomized controlled trial of 76 patients (20 sham treated), 14% had persistent paresthesia or numbness at 12 months, 9% had a gait disturbance, 4% had limb dysmetria, 2% had limb weakness, and 2% had disequilibrium [46]. These percentages were much higher immediately after surgery (36%, 12%, 4%, and 9%, respectively), and 5 thalamotomy procedures were interrupted or suspended because of pain, nausea, vertigo, or vomiting. Dysarthria and dysphagia each occurred in one patient and took 12 months to resolve. Eight of 27 patients who had PSA ablations experienced gait impairment, which failed to resolve in one patient [56,57].

3.7. Adverse effects of stereotactic radiosurgery

Widely varying rates of permanent neurologic deficits have been reported, and an estimated 10% of patients exhibit excess lesion formation in response to the radiation, which is usually associated with significant morbidity [58]. Procedure-related deaths have also occurred [100]. The most commonly reported deficits are the same as those of FUS and radiofrequency thalamotomy. Many deficits resolve with time. Proponents of SRS believe it is safer than DBS and other forms of thalamotomy, and they argue that this method is at least as effective, with lower rates of loss of efficacy [47,74]. A recent meta-analysis supports the efficacy of this procedure compared to radiofrequency ablation and FUS, but the response to therapy is more variable [12]. Detractors point out that lesion location, efficacy, and adverse effects cannot be confirmed intraoperatively because imaging and clinical effects take at least 3 months to develop. Patients must be observed at least 18 months for procedure-related adverse effects [100]. About 20% of patients fail to exhibit any improvement in tremor [47,74,100].

3.8. Adverse effects of deep brain stimulation

3.8.1. Perioperative adverse effects

The National (Nationwide) Inpatient Sample (NIS) database of hospital admissions in the United States was searched for inpatient complications in patients who underwent DBS or ablative procedures from 1999 to 2008 (4096 PD patients, 1210 ET and 158 dystonia; ages 19–92, mean 63.7) [101]. The move from ablative procedures to DBS was associated with no significant change in inpatient mortality or morbidity (e.g. infarction and hemorrhage). Hemorrhage and stroke were more likely to occur in Parkinson patients (1.98%) than ET (0.74%). Other studies also have found that DBS surgery is safer in ET than in PD [102]. A search of the MarketScan database produced 661 ET patients (56.9% male) that underwent DBS surgery between 2000 and 2009, and 7.1% experienced at least one complication within 90 days of surgery [44]. The most common complications were wound infection (3.0%), pneumonia (2.4%), hemorrhage (1.5%), and pulmonary embolism (0.6%). Lead replacement or revision occurred in 0.3% of patients, and generator removal or revision occurred in 1.1% of patients. One (0.2%) patient died within 90 days of DBS. There was no statistical relationship of these complications to patient age, ranging from <50 to 90 years, although only 5.6% of patients were 80–90 years old.

Intracerebral hemorrhage is the most feared perioperative complication and has been seen with post-op imaging in as many as 6.5% of a mixed population of patients (ET, PD, dystonia, and other) [103,104]. Nearly all are asymptomatic or only transiently symptomatic [105]. Cortical or subcortical infarction occurs in less than 1% and is usually asymptomatic [105]. There is conflicting opinion whether repeated electrode passes during microelectrode mapping increases the risk of hemorrhage [103,105–110], but the majority opinion is that microelectrode mapping carries some increase in risk. Hemorrhage can occur when target location is confirmed only with macroelectrode stimulation [110]. A meta-analysis of published procedures in which electrodes or inoculation probes were inserted into the brain, not limited to surgery for ET, revealed a 1.57% (95% CI, 1.26%–1.95%) risk of intracerebral hemorrhage per trajectory for all probes and a 2.0% risk for microelectrodes [95% CI, 1.2–3.4] [111]. The per-trajectory adjusted risk of mortality was 0.14% (95% CI, 0.07%–0.29%), and the rate of permanent or serious adverse effects was 0.41% (95% CI, 0.28%–0.60%). Microelectrode recordings were associated with an increased risk, but gender and age were not. One study found that the insertion of multiple electrodes simultaneously was the main risk factor for hemorrhage [112]. The risk of hemorrhage is probably increased in hypertensive patients [110].

Perioperative infection is the most common serious adverse event in DBS surgery. The brain lead, lead extension cable, and implantable pulse generator are each susceptible to infection. Infection around the pulse generator is most common. Perioperative infection has been reported in 0–15% of DBS surgeries for all indications combined [103,105]. In one large series, the risk of hardware-related infection per DBS lead was 2.5%, with Staphylococcus aureus and other skin flora being the most common pathogens [113]. Most infections require at least partial hardware removal [103]. If infection extends over the brain lead, the electrode must be removed to prevent brain infection and then reimplanted after the infection is clear. In one large series, sparing of the electrode occurred in 64% of patients, and brain infection did not occur [113]. The prevention and management of infections are reviewed elsewhere [113].

In mixed populations of DBS patients (ET, PD, dystonia, and other), intraoperative seizures have been reported in 0.3–2.3%, and postoperative seizures in 0.4–9.1% [105]. A review of the

published literature in 2009 revealed an estimated perioperative seizure risk of 2.5% and a 0.5% risk of long-term epilepsy [114,115].

3.8.2. Adverse effects of electrical stimulation

We reviewed 16 case series for adverse effects of DBS programming in ET [64,70,71,76–78,83,86,88,91,103,116–119]. The data from most of these studies came from retrospective chart reviews. Four studies [70,83,88,118] that collected data prospectively reported a much higher incidence of adverse effects, suggesting that stimulation-induced adverse effects are generally underreported. Paresthesia, muscle contraction, dysarthria, limb ataxia, gait disturbance, and disequilibrium are common side effects of DBS in Vim thalamus and the PSA. Stimulation-induced side effects occur in virtually all patients, depending on the lead configuration and stimulation parameters, and side effects frequently limit the intensity of stimulation needed to control tremor. It is unclear from the literature what percentage of patients endures stimulation-induced adverse effects after programming optimization, but 25–50% is a fair estimate [83,88,118]. Such side effects are more common in patients with bilateral surgery [83,88,118].

Gait and balance problems are common after bilateral and unilateral Vim DBS and may not resolve when DBS is turned off [120]. Persistent gait and balance impairment have been reported in as many as 58% of patients, more so in patients with bilateral DBS and in patients with preoperative gait and balance problems [121]. These problems may be progressive and irreversible or may not reverse without a long stimulation holiday lasting weeks, suggesting deleterious neuroplastic change in the cerebellum [122]. Disabling dystonia also has been described [88].

Speech disturbances are common. A review of the published literature in September 2014 produced an estimated incidence of 12.3% (95% CI: 8.0–18.5) after unilateral surgery and 41.4% (95% CI: 26.0–58.6) after bilateral surgery for ET, which is higher than reported for radiofrequency thalamotomy [99]. Many patients can reduce their dysarthria by turning their stimulator(s) down, but this results in greater tremor.

3.8.3. Hardware-related complications

Jitkritsadakul and coauthors [123] reviewed the DBS literature to estimate the incidence of hardware-related complications in the treatment of any condition, experimental or approved. They were not able to estimate risk for ET only. Nevertheless, the most common complications (% of patients) were infections (5.12%), lead migration (1.60%), fracture or failure of the lead (1.46%) or extension cable (0.73%), IPG malfunction (1.06%), and skin erosions without infections (0.48%). Fractures between the electrode lead and connecting wire were common until it became general practice to place this connection behind the ear, above the mastoid [103]. Modern IPGs are far more reliable than early devices [123]. Discomfort around the implant site (0.61%), IPG dislocations (0.29%), subcutaneous seroma (0.26%), and tethering of extension cable (0.12%) also occur. These complications can be corrected but usually require additional surgery and hardware replacement.

3.8.4. Optimum target location

Stereotactic ventrolateral thalamotomy for tremor was first conducted by Hassler and Riechert in the early 1950s [124,125]. The cerebellar receiving nucleus Vim was viewed as the optimum target until Velasco and others drew attention to the cerebellothalamic fiber tract in the PSA [126]. There is now a growing consensus that the most effective DBS site is the upper PSA where the cerebellothalamic fibers enter Vim [127,128], but for some patients, the best site for DBS is within Vim, above the AC-PC line [84,129]. We reviewed 13 studies in which imaging methods were used to locate the AC-PC coordinates of the most effective electrode contacts for DBS (Table 4) [82,92,116,126,129–137]. There was considerable variability among patients, resulting in extensive overlap in

Table 4. Computed coordinates of DBS electrode contacts producing optimum stimulation results.

Study and number of patients/ leads	Anatomical target and treatment	Method of coordinate measurement	Mean ±SD electrode coordinates (mm)			
			Lateral distance (AC-PC line)	AP distance (anterior to PC)	AP distance (posterior to MCP)	Vertical distance from AC-PC plane
Barbe [130] 21/40	Vim DBS	Stereotactic skull X-ray Post-op CT	11.3 ± 1.6		7.2 ± 1.7	−1.4 ± 1.2
Blomstedt [116] 21/31	PSA DBS	Post-op CT	11.6 ± 1.8		6.3 ± 1.6	−3 ± 2.3
Fenoy [129] 20/40	CTT DBS	DTI tractography	R 13.5 ± 1.8 L 13.5 ± 1.8		R 5.8 ± 1.6 L 6.3 ± 1.6	R 1.7 ± 2.5 L 2.9 ± 2.7
Groppa [138] 6/12	Vim DBS	Post-op MRI	12.9 ± 1.6		6.8 ± 1.3	−1.8 ± 0.7
Hamel [131] 8/16	Vim DBS	Stereotactic skull X-ray Post-op MRI	12.7 ± 1.4		7.0 ± 1.6	−1.5 ± 2.0
Murata [82] 8/8	PSA DBS	Post-op MRI	10.9 ± 0.8		7.6 ± 1.2	−3.9 ± 1.7
Papavassiliou [84] 37/57	Vim DBS	Post-op MRI	12.8 ± 1.7	7.8 ± 1.5	5.7 ± 1.6	0.8 ± 2.5
Pouratian [146] 6/12	Vim DBS	Post-op MRI, DTI tractography	14.0 ± 1.5	7.8 ± 1.8		+1.3 ± 1.3
Sandvik [135] 36/44	19 Vim/25 PSA DBS	Post-op CT	12.1 ± 1.8		5.5 ± 1.9	−1.2 ± 2.9

AC: anterior commissure; AP: anteroposterior; CT: computed tomography; CTT: cerebellothalamic tract; DBS: deep brain stimulation; DTI: diffusion tensor imaging; L: left; MCP: mid-commissural point; MRI: magnetic resonance imaging; PC: posterior commissure; Post-op: post-operative; PSA: posterior subthalamic area; R: right; Vim: ventralis intermedius

the spatial distribution of effective and ineffective electrode contacts, especially above and below the AC-PC line (note the standard deviations of optimum electrode coordinates in Table 4). The reasons for this variability are not clear.

The PSA is located immediately below Vim, lateral to the red nucleus, and posteromedial to the subthalamic nucleus [135,139]. The PSA contains the cerebellothalamic tract and caudal zona incerta (cZi) (Figure 2). The medial lemniscus is located immediately behind this target area [139,140]. The anteroposterior thickness of Vim at its inferior border is about 3 mm [140]. The thickness of the cerebellothalamic tract as it enters Vim is 2–3 mm, and the DBS electrodes have a diameter of 1.27 mm [141]. Velasco found that insertion of a recording electrode into the PSA typically produces a so-called microlesion effect in which tremor is greatly reduced [126]. Given the diameter of the DBS electrode, it is not surprising that its insertion into PSA commonly produces a microlesion effect.

Vim versus PSA is not the only debate; cZi versus the cerebellothalamic tract is also debated in regard to the optimum site of stimulation. However, it is doubtful whether specific targets in the PSA can be stimulated or ablated with adequate consistency and accuracy to test whether one subthalamic target is better than another. Even when cZi is targeted, the cerebellothalamic tract may be the critical structure that is stimulated or ablated and vice versa. In one study, stimulation-induced side effects in PSA DBS did not differ with electrode location within the PSA [142]. This finding is consistent with the small compact anatomy of this region [140], the electrode diameter (1.27 mm), and the spheroidal volume of tissue activation extending 1–3 mm from the electrode [143].

Defining the path of connectivity from the cerebellothalamic tract to motor and premotor cortex could be a better approach to defining the optimum stereotactic target in a particular patient. To this end, diffusion-tensor MRI tractography-based maps of thalamic targets have been employed postoperatively to identify the most effective thalamic target site for Vim DBS and thalamotomy. There is disagreement among studies as to whether thalamic connectivity with motor cortex [144,145] or premotor cortex (lateral premotor cortices and medial supplementary motor cortex) [146,147] is most important, and connectivity with the cerebellar dentate nucleus is also predictive of surgical success [145]. A tractography approach could prove useful in pre-operative target identification [148,149], but the methods of diffusion tractography for this purpose are still being developed and require increased imaging time and hardware requirements [145,149–151]. One feasibility study of 5 patients produced poor tremor control in 1, and stimulation-induced side effects limited IPG programming in 3 [145].

The subthalamic nucleus was found to be an effective target for ET in two small studies but not as effective as the PSA [152,153]. Nevertheless, some patients receiving the diagnosis of ET actually have tremor with focal or segmental dystonia, and STN may make sense in these patients [154,155] and in patients with both ET and PD [156].

The long-term success rate of reoperation for suboptimal electrode placement is unknown. There are no consensus criteria for when a patient should undergo a second surgery [157]. Some electrodes are ineffective even though they appear to be in the desired location. In a large case series from one center, 3 of 70 electrodes (4.3%) were replaced due to lack of efficacy [103]. Ellis and coworkers retrospectively reviewed 7 ET patients that underwent replacement surgery because of inadequate tremor control [157]. The most effective electrode contact was moved 2.3–13.7 mm (mean 6.1 mm), and all 7 patients experienced significant improvement.

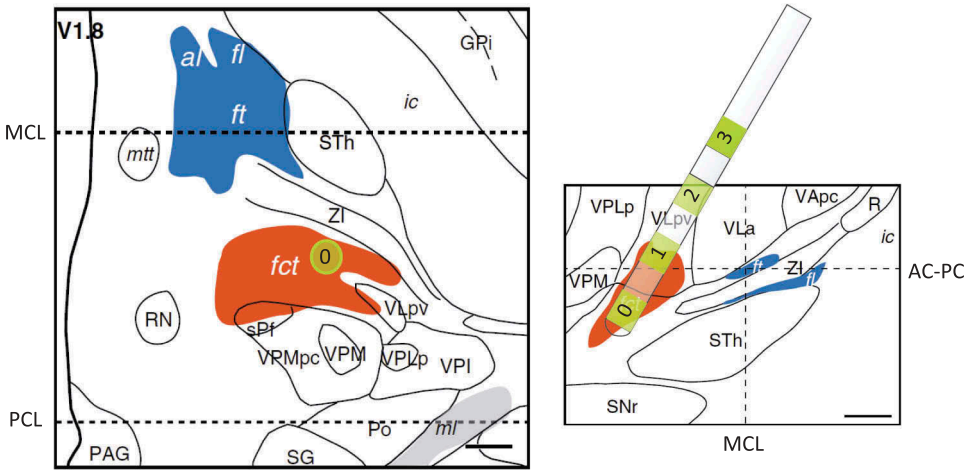

Figure 2. Horizontal section of the subthalamic area 1.8 mm below the plane of the AC-PC line (left) is shown with a sagittal section 11.7 mm lateral to the midline (right). Also shown is a typical quadripolar electrode trajectory extending through VLpv (a.k.a., Ventralis intermedius, Vim) into the posterior subthalamic area. Note the electrode diameter and size of electrode contacts relative to neighboring anatomical structures. The volume of tissue activation extends 1–3 mm from the cathode electrode contact(s), depending on the voltage/current and width of the electrical pulses. Scale bars in lower right of each figure are 2 mm. The dashed lines are the midcommissural (MCL), posterior commissural (PCL), and AC-PC lines. Adapted from Gallay et al. [140].

AC: anterior commissure; Al: ansa lenticularis; fct: cerebellothalamic tract; fl: fasciculus lenticularis; ft: fasciculus thalamicus; GPi: globus pallidus interna; ic: Internal capsule; ml: medial lemniscus; mtt: mamillothalamic tract; PAG: periaqueductal gray; PC: posterior commissure; Po: posterior nucleus; R: reticular thalamic nucleus; RN: red nucleus; SG: supragenicular nucleus; SNr: substantia nigra pars reticulata; sPf: subparafascicular nucleus; STh: subthalamic nucleus; VApc: ventralis anterior parvocellularis; VLa: ventralis lateralis anterior; VLpv: ventralis lateralis posterior ventral; VPI: ventralis posterior inferior; VPLp: ventralis posterior lateralis posterior; VPM: ventral posterior medial nucleus; VPMpc: ventralis posterior medialis parvocellular division; ZI: zona incerta.

3.9. Loss of efficacy (tolerance)

It is common for DBS patients to experience loss of efficacy, even during the first few months following surgery [151,158]. There are several possible reasons for this: tolerance to stimulation, disease progression, suboptimal lead placement, and loss of microlesion effect. Tolerance to stimulation is most controversial. Loss of efficacy following ablative surgery also occurs [72].

Many patients require increasing strengths of stimulation and experience reduced control of tremor during the first 12 months after surgery and thereafter [136,159]. In one study, 70% of post-operative stimulator adjustments were performed to improve tremor control, while only 15% were needed for eliminating side effects [86]. Hariz et al. reported an average 3.5 clinic visits for stimulator adjustments during the first 12 months postop [159], and Shih and coworkers found that 33 of 45 patients (73.3%) reported waning benefit at a mean time of 18.8 ± 15.1 months (range 3–75 months) following lead implantation [136]. Patients with and without waning benefit frequently do not differ statistically in lead location, even though gradual loss of efficacy is often attributed to suboptimal lead placement [84,133,136].

The reported incidence of tolerance in DBS has varied from nil [78] to common [136]. The presence of tolerance is indicated by improved tremor control after stimulation is turned off for hours, days or weeks [160,161] and by loss of efficacy days or weeks after IPG (implantable pulse generator) optimization [151,162]. Patients with tolerance experience loss of efficacy and require multiple stimulator adjustments during the first year following surgery. This rate of decline is far too fast to be explained by disease progression [163]. Turning the IPG off at night is believed to reduce or prevent tolerance [95,159,164], but this has never been proven in a controlled study. Turning the pulse generators off can be difficult and distressing for patients with severe tremor, particularly for the 10–30% of patients with rebound tremor [159,161]. Switching between two slightly different predefined electrode settings might be effective in reducing tolerance [162,165].

It is unclear how often programming parameters were acutely optimized in the follow-up examinations of published clinical studies, but this was the practice in many studies [30,60,64,65,67]. In addition, many groups told patients to turn their stimulators off at night and come to clinic with stimulators off [59,62,65,67,92,116,132]. These practices could mask the presence of tolerance because turning the pulse generator off and then on reduces tremor in patients with tolerance.

Leads with lost efficacy are occasionally relocated in another surgical procedure with all of the attendant risks of the original surgery. The long-term benefit of relocating leads has not been studied [166]. In some cases, an ineffective electrode was used to perform radiofrequency thalamotomy [167–169], but the results of this approach have not been studied prospectively and are not always satisfactory. The implantation of parallel dual leads in Vim and Vop has also been tried with reported success [170], the rationale being that tolerance involves the expansion of tremorogenic oscillation within the thalamus and cortical connections [137].

Loss of efficacy following ablative therapy may be treated by additional ablation or DBS. We found no studies of the best approach.

4. Conclusions

DBS and SRS, FUS and radiofrequency ablations are capable of reducing ET by more than 80% and are far more effective than any available drug. These surgical methods produce comparable short-term reductions in tremor. Therefore, choice of methodology should be based primarily on expense, safety, and long-term efficacy.

Radiofrequency ablation was largely replaced by DBS due to the high risk of permanent neurological deficits following bilateral radiofrequency thalamotomy and subthalamotomy [35,72]. Most patients with ET have bilateral tremor and many have significant axial tremor that may require bilateral surgery. Bilateral DBS is believed by many to be safer than bilateral FUS and SRS, but this impression is based largely on results from old radiofrequency thalamotomy case series. The safety of bilateral FUS and SRS is unclear, and some investigators believe these methods could be as safe as bilateral DBS [50,171]. Recent cost-effectiveness analyses revealed that unilateral FUS and gamma knife thalamotomy are superior to DBS [172,173].

There is only one randomized, sham-controlled, double-blind study of surgery for ET, the pivotal trial of FUS thalamotomy [46]. Only a few studies employed blinded evaluations for efficacy and systematic prospective collection of adverse effects. Studies comparing one procedure with another are needed.

Tolerance to DBS is a significant problem and is readily demonstrated by improved tremor control after the pulse generators have been turned off overnight or for as little as 30 min. Patients should be warned of the possible development of tolerance and should be counseled to turn off their stimulators at night, even though the efficacy of this approach has not been proven. This practice will at least prolong battery life substantially.

There is an emerging consensus that the PSA is the optimum target for tremor suppression by DBS, FUS and SRS. The critical structure, cerebellothalamic tract or cZi, is uncertain, and it seems doubtful that current technology is sufficient to selectively target either target alone.

5. Expert commentary

The key weaknesses in clinical management are the uncertainties of optimum target location, the high incidence of adverse effects, and the loss of efficacy of ET surgery over time. DBS is expensive, and it requires IPG replacements due to battery failure and followup programming adjustments in stimulation parameters. The relative safety and efficacy of bilateral DBS, FUS and SRS requires further study. Systematic collection of efficacy data and adverse effects is needed in the context of controlled clinical trials. The severity of adverse effects should be documented systematically, as in the study of Burdick and coworkers [118]. ET is a monosymptomatic disorder, and new symptoms or signs (e.g. dysarthria, impaired balance, sensory

symptoms) caused by surgery may be alarming to ET patients, even when they are mild.

MR diffusion tractography-based network analyses will continue to produce important insights into the variability of outcomes among individual patients receiving DBS or ablative therapy for ET and should improve our understanding of the mechanisms of these surgical procedures. However, a crucial question is whether preoperative diffusion tractography can be used to identify anatomical targets with greater accuracy and efficacy than current atlas-based methods.

New DBS electrodes have multiple small contacts, oriented longitudinally and circumferentially, that allow more precise directional stimulation of surrounding tissue than conventional electrodes with four circumferential contacts that are 1.5 mm wide and spaced 0.5 or 1.5 mm apart [174]. These new electrodes have the potential of producing more precise targeting, resulting in less tremor and side effects but also entail greater programming time, complexity, and cost [174]. Controlled studies are underway [175].

It is commonly stated that, due to the immediate strong effect of DBS in ET patients, a truly blinded analysis of the preoperative to the postoperative state is probably impossible. The efficacy of DBS and ablative therapy is no longer in question. The main research questions at this time are 1) the relative safety, efficacy and expense of DBS, SRS, and FUS performed unilaterally and bilaterally, 2) the relative safety and efficacy of thalamic versus PSA targeting, 3) the relative safety and efficacy of atlas-based versus diffusion tractography-based DBS targeting, and 4) the need for intraoperative microelectrode recordings and macroelectrode stimulation in awake patients to identify the optimum anatomical target. Each of these questions provides opportunities for randomized patient allocation, blinded patient evaluations, and prospective systematic collection of adverse effects. However, for each of these four questions, the difference in efficacy may be so small that a very large number of patients will be needed to reveal statistically significant differences in efficacy. For example, using the reported data from the uncontrolled study of Blomstedt and coworkers (Table 2 in [59]), we computed the percentage reductions in head, voice, upper extremity, and drawing/pouring tremor to be 42, 45, 80 and 82% for Vim DBS and 31, 21, 84 and 84% for PSA DBS. Thus, it is likely that impractically large patient populations will be needed to show an efficacy advantage for one of these targets. Nevertheless, the systematic prospective blinded collection of long-term efficacy data (tremor ratings, ADL, quality of life and patient satisfaction), adverse events, and IPG programming requirements would be invaluable.

Average percentage reductions in tremor may not accurately reflect improvement that is regarded by the patient as good or meaningful. A reduction in tremor from grade 4 (>20 cm) to grade 2 (1–3 cm) on the TETRAS scale is at least an 84% reduction in tremor amplitude, which is impressive, but a patient with 20 cm kinetic tremor would still have a disabling 3.2 cm tremor after an 84% reduction. The minimum clinically important change for ET has not been determined, and change per se may not be as important to patients as the final amplitude of tremor. There is some evidence to suggest that truly successful treatment is a reduction of tremor to <1 cm, which is grade 1 or 1.5 on TETRAS or FTM [10]. Better documentation of this magnitude of change is needed in future studies.

ET is a syndrome, not a specific disease. By definition, patients with ET exhibit tremor and no other neurologic signs [1]. However, it is clear that subtle signs are often missed or dismissed as insignificant, resulting in misdiagnosis [28]. Careful phenotyping of each patient is needed to understand the heterogeneous genetics, pathology, pathophysiology and response to treatment, and ET researchers are now forming international collaborations to accomplish such phenotyping in large patient cohorts [3]. Subtle or questionable dystonia, myoclonus, ataxia, bradykinesia, and rigidity must be carefully documented and correlated with results from surgery and from structural and functional imaging studies. Centralized registries that house information on clinical outcomes, baseline and post-operative imaging data and that contain tools for multi-center data sharing and analysis should be considered in order to advance our understanding of thalamic network connectivity among various surgical methods.

Space does not permit us to address the controversy of whether microelectrode recording and macrostimulation are needed to confirm target location in DBS surgery for ET. Vim cannot be distinguished from neighboring thalamic nuclei on MRI or CT, and the cerebellothalamic tract is visible only with MR diffusion tractography. Nevertheless, improved imaging of Vim and the cerebellothalamic tract could obviate the need for microelectrode recording to map the target area and for macrostimulation to confirm clinical response [176]. Elimination of microelectrode recording and macrostimulation would allow surgery to be performed under general anesthesia, using intraoperative CT or MR imaging to confirm optimum electrode location. We found one published report of this approach in ET [177]. Financial cost may be less for patients undergoing DBS surgery asleep [178].

6. Five-year view

We searched the ClinicalTrials.gov online database for ET surgical studies in order to predict the following advances.

Prospective data will likely emerge regarding the safety and efficacy of bilateral FUS and SRS, including the incidence of adverse effects and incomplete sonication/radiation.

Traditional atlas-based stereotactic surgery of Vim/PSA using intraoperative macrostimulation confirmation of target location is being compared with surgery under general anesthesia using a cerebellothalamic tract target computed with MR diffusion tractography [179]. Patients are randomly allocated to the two surgical groups, and video-recorded exams are assessed by blinded raters. We will undoubtedly see continued efforts to refine MRI network-based stereotactic targeting.

Barbe and coworkers have designed a double-blind crossover trial comparing Vim and PSA, videotaping the preoperative and postoperative tremor exams for blinded analysis by an independent rater [180].

Finally, many technological advances in DBS delivery are being developed or are now being tested for safety and efficacy [176]. These advances include electrodes with greater

numbers of contacts to better control the size and shape of the volume of brain stimulation and IPGs with more flexible programming options that would allow stimulation patterns other than continuous rhythmic stimulation. The increased programming complexity, time and expense must be weighed against demonstrated clinical benefits. Stimulation patterns theoretically could be developed that would suppress tremor more efficiently and possibly have a beneficial neuroplastic effect on the oscillating nerve network, leading to a reduction in tremorogenesis. Studies are also underway in which novel stimulation patterns and alternating stimulation settings are being investigated to improve tremor suppression and reduce tolerance. To reduce the need for patient programming, adaptive closed-loop DBS is being developed in which DBS is delivered in response to electrical activity recorded from brain or from motion sensors on a body part.

Key issues

- Deep brain stimulation and ablative surgery in ventrolateral thalamus and the posterior subthalamic area have indisputable efficacy in the treatment of ET, producing benefit that far exceeds any medication for ET.
- The relative long-term efficacies of deep brain stimulation and ablative surgery are unclear. Significant loss of efficacy from all procedures occurs over time in many patients.
- There are no evidence-based guidelines for patient selection. Comorbidities rather than patient age are the principal concern.
- The relative safety of deep brain stimulation and ablative surgery has not been determined in controlled comparative trials. Risks of adverse effects are greater with bilateral surgery.
- Conventional lead location using atlas-based stereotactic coordinates and intraoperative electrophysiology could be supplanted by preoperative diffusion tractography-based target location and intraoperative imaging to confirm electrode location, allowing surgery to be performed under general anesthesia.
- The technologies of deep brain stimulation, focused ultrasound, and stereotactic radiosurgery are rapidly advancing.

Acknowledgment

This paper was supported in part by a grant from the Illinois-Eastern Iowa District Kiwanis Neuroscience Foundation.

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Declaration of interest

R Elble has performed consultant work for Biohaven, Cadent, Cavion, and Sage, and he was a paid reviewer of patient video exams in a study funded by InSightec. He serves on the medical advisory board of the International Essential Tremor Foundation. He is the Medical Director of Illinois-Eastern Iowa District Kiwanis Neuroscience Foundation, and he receives a research grant from this foundation. L Shih was a paid rater of patient video exams, a study funded by InSightec, and is a member of the medical advisory board of the International Essential Tremor Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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