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Practice Parameter: Therapies for essential tremor

Report of the Quality Standards Subcommittee of the American Academy of Neurology

T.A. Zesiewicz, MD; R. Elble, MD, PhD, FAAN; E.D. Louis, MD, MS, FAAN; R.A. Hauser, MD, MBA, FAAN; K.L. Sullivan, MSPH; R.B. Dewey, Jr., MD, FAAN; W.G. Ondo, MD; G.S. Gronseth, MD; and W.J. Weiner, MD, FAAN

Abstract—*Background:* Essential tremor (ET) is one of the most common tremor disorders in adults and is characterized by kinetic and postural tremor. To develop this practice parameter, the authors reviewed available evidence regarding initiation of pharmacologic and surgical therapies, duration of their effect, their relative benefits and risks, and the strength of evidence supporting their use. *Methods:* A literature review using MEDLINE, EMBASE, Science Citation Index, and CINAHL was performed to identify clinical trials in patients with ET published between 1966 and August 2004. Articles were classified according to a four-tiered level of evidence scheme and recommendations were based on the level of evidence. *Results and Conclusions:* Propranolol and primidone reduce limb tremor (Level A). Alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate are probably effective in reducing limb tremor (Level B). Limited studies suggest that propranolol reduces head tremor (Level B). Clonazepam, clozapine, nadolol, and nimodipine possibly reduce limb tremor (Level C). Botulinum toxin A may reduce hand tremor but is associated with dose-dependent hand weakness (Level C). Botulinum toxin A may reduce head tremor (Level C) and voice tremor (Level C), but breathiness, hoarseness, and swallowing difficulties may occur in the treatment of voice tremor. Chronic deep brain stimulation (DBS) (Level C) and thalamotomy (Level C) are highly efficacious in reducing tremor. Each procedure carries a small risk of major complications. Some adverse events from DBS may resolve with time or with adjustment of stimulator settings. There is insufficient evidence regarding the surgical treatment of head and voice tremor and the use of gamma knife thalamotomy (Level U). Additional prospective, double-blind, placebo-controlled trials are needed to better determine the efficacy and side effects of pharmacologic and surgical treatments of ET.

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Background and justification. Essential tremor (ET) is a common adult tremor disorder, with prevalence estimates from population studies ranging from 0.4% to 5%.[1,2] The incidence and prevalence of ET increase with advancing age.[2]

ET is characterized by the presence of postural and kinetic tremor.[3] In classic ET, upper limbs (~95% of patients) and less commonly the head (~34%), lower limbs (~30%), voice (~12%), tongue (~7%), face (~5%), and trunk (~5%) exhibit a postural or kinetic tremor.[4] ET has been referred to as a benign condition because of the perception that it does not reduce life expectancy or cause symptoms besides tremor and impaired tandem walking. However, ET may cause substantial physical and psychosocial disability,[5] and it is unclear whether ET is associated with additional comorbid symptoms.[6] Tremor amplitude gradually increases over time, and patients frequently experience increasing difficulty with writing, drinking, eating, dressing, speaking, and other fine motor tasks.[5]

ET is a clinical diagnosis. Criteria for definite and probable ET include abnormal bilateral postural or ki-

From the Department of Neurology and Parkinson's Disease and Movement Disorders Center (Drs. Zesiewicz and Hauser, and K.L. Sullivan), University of South Florida, Tampa; Department of Neurology (Dr. Elble), Southern Illinois University School of Medicine, Springfield; GH Sergievsky Center and Department of Neurology (Dr. Louis), College of Physicians and Surgeons, Columbia University, New York, NY; University of Texas Southwestern Medical Center (Dr. Dewey), Dallas; Department of Neurology (Dr. Ondo), Baylor College of Medicine, Houston, TX; Department of Neurology (Dr. Gronseth), University of Kansas Medical Center, Kansas City; and Department of Neurology (Dr. Weiner), University of Maryland School of Medicine, Baltimore.

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Address correspondence and reprint requests to the American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116.

netic tremor of the hands in the absence of other neurologic signs. Many clinicians accept isolated tremor of the head if there is no evidence of dystonia.[3]

Propranolol and primidone are commonly used to treat ET, although propranolol is the only medication that is approved by the Food and Drug Administration (FDA) for this purpose. It is estimated that at least 30% of patients with ET will not respond to propranolol or primidone.[7] Alcohol reduces tremor amplitude in 50 to 90% of cases,[8-10] but tremor may temporarily worsen after the effect of alcohol has worn off.[11] Invasive therapies including surgical procedures may provide clinical benefit in cases of refractory tremor.

Mission statement. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology is charged with developing practice parameters for physicians and neurologists by providing specific recommendations for clinical decisions based on analysis of evidence. The selection of topics for which practice parameters are used is based on prevalence, frequency of use, economic impact, membership involvement, controversy, urgency, external constraints, and resources required.

Panel selection and literature review process. Neurologists with expertise in ET were invited by the QSS to perform the review. Computer-assisted literature searches were conducted for relevant English language articles pertinent to ET and for medications that are available in the United States. Databases searched include MEDLINE, EMBASE, Science Citation Index, and CINAHL between 1966 and 2004. A total of 502 articles pertaining to treatment and management of ET were published between 1966 and August 2004, and all search titles and abstracts were analyzed for content and relevance by individual committee members. Articles were accepted for further review if they consisted of double-blind controlled trials, open-label studies, case series, and case reports. There were 211 articles that were accepted for further review. Each of these articles was classified by two panel members using a four-tiered classification scheme that was developed and approved by the QSS (Appendix 1). Analysis of evidence is summarized in tables 1 and 2.

The following key words and phrases were used in the initial search and were paired with the term "essential tremor." Both brand and generic names were used in the searches (generic names are listed here only): acetazolamide, alprazolam, amantadine, aminophylline, antiepileptics, arotinolol, atenolol, atypical neuroleptics, B-adrenergic blockers, benzodiazepines, botulinum toxin A, botulinum toxin B, calcium channel blockers, carbonic anhydrase inhibitors, chemodenervation, clinical trials, clonazepam, clonidine, clozapine, deep brain stimulation (DBS), gabapentin, gamma knife surgery, glutethimide, hypnotics, isoniazid, management, methazolamide, metoprolol, mirtazapine, nadolol, nicardipine, nifedipine, nimodipine, olanzapine, phenobarbital, pindolol, primidone, propranolol, propranolol long-acting, quetiapine, research design, sotalol, stereotactic surgery, thalamotomy, theophylline, therapy, topiramate, trazodone, verapamil, VIM thalamic stimulation. Articles dedicated to dystonia, dystonic tremor, myoclonus, cerebellar tremor, "atypical tremor," Parkinson disease (PD), parkinsonism, orthostatic tremor, palatal tremor, primary writing tremor, animal models of ET, pathophysiology, genetics, epidemiology, cognitive dysfunction, quality of life, social phobia, and neuropsychiatric testing in ET were excluded from the review.

Clinical questions. *Pharmacologic treatment for ET.* What are the safety, tolerability, and efficacy of pharmacologic agents in treating ET? Which drug should be used for initial treatment of ET? Is combined treatment with primidone and propranolol better than monotherapy? Is there evidence for sustained benefit of pharmacologic treatment of ET? Do patients with ET benefit from chemodenervation with botulinum toxin type A or B?

Surgical treatment for ET. What is the efficacy of thalamotomy in treating contralateral limb tremor in patients with ET? What is the efficacy of deep brain stimulation (DBS) of the thalamus in treating tremor in patients with refractory ET? Should thalamotomy or DBS of the thalamus be the procedure of choice in patients with medically refractory ET? What are the indications for bilateral versus unilateral surgical procedures in ET?

Analysis of the evidence: Pharmacologic treatment of ET. *1. What are the safety, tolerability, and efficacy of pharmacologic agents in treating ET?* 1A. Pharmacologic agents with Level A recommendation. *Propranolol (Inderal).* Propranolol is a nonselective beta-adrenergic receptor antagonist. Twelve class I studies found that propranolol was efficacious in treating limb tremor in ET, and tremor magnitude as measured by accelerometry was reduced by approximately 50% (see table 1). Nine of the class I studies reported a mean dose of propranolol of 185.2 mg/day. Although the remaining three studies did not report a mean dose, the dose range for all studies was 60 to 320 mg/day. Side effects occurred in 12% to 66% of patients and included lightheadedness, fatigue, impotence, and bradycardia.

Contrary to earlier recommendations, propranolol may be used in patients with stable heart failure due to left ventricular systolic dysfunction, unless there are clear contraindications to its use, such as unstable heart failure.[12] It is recommended that physicians who are considering treating cardiac patients with propranolol follow the recommendations of the *American Journal of Cardiology* consensus statement (or the equivalent) for the complete indications and contraindications of its use,[12] or consult with a cardiologist.

Propranolol LA (Inderal LA). Propranolol is available as a long-acting (LA), once daily preparation. One class I[13] and one class II[14] study found that

Table 1 *Oral pharmacologic agents in the treatment of essential tremor*

Intervention	Level of evidence	No. of studies	Cohort size	Dose	Adverse events severity*	Magnitude of effect
Primidone (Mysoline)	A	12	218	Up to 750 mg/d	Mild-moderate (sedation, drowsiness, fatigue, nausea, giddiness, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, acute toxic reaction)	50% Mean improvement by CRS and accelerometry
Propranolol (Inderal)	A	32	533	60–800 mg/d	Mild to moderate (reduced arterial pressure, reduced pulse rate, tachycardia, bradycardia, impotency, drowsiness, exertional dyspnea, confusion, headache, dizziness)	50% Mean improvement by CRS and accelerometry
Propranolol LA (Inderal LA)	A	2	33	80–320 mg/d	Mild (skin eruption, transient dizziness)	30–38% Improvement by accelerometry
Alprazolam (Xanax)	B	2	46	0.125–3 mg/d	Mild (fatigue, sedation; potential for abuse)	25–34% Mean improvement in CRS compared to baseline
Atenolol (Tenormin)	B	5	79	50–150 mg/d	Mild-moderate (lightheadedness, nausea, cough, dry mouth, sleepiness)	25% Mean improvement by CRS and 37% Mean improvement by accelerometry compared to baseline
Gabapentin (Neurontin) monotherapy	B	3	61	1,200–1,800 mg/d	Mild (lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath)	77% Improvement by accelerometry and 33% Improvement by CRS compared to baseline
Sotalol (Sotacor)	B	3	50	75–200 mg/d	Mild (decreased alertness)	28% Mean improvement by CRS compared to baseline
Topiramate (Topamax)	B	5	335	Up to 400 mg/d	Mild (appetite suppression, weight loss, paresthesias, anorexia, concentration difficulties)	22–37% Mean improvement in CRS compared to baseline
Clonazepam (Klonopin)	C	3	44	0.5–6 mg/d	Mild-moderate drowsiness	71% Mean improvement by accelerometry and 26–57% improvement in CRS compared to baseline
Clozapine (Clozaril)	C	2	27	6–75 mg/d	Mild (sedation); Severe (potential agranulocytosis)	45% Mean improvement by accelerometry
Nadolol (Corgard)	C	1	10	120–240 mg/d	None	60 to 70% Improvement by accelerometry in patients who had previously responded to propranolol
Nimodipine (Nimotop)	C	1	16	120 mg/d	Mild (headache, heartburn)	53% Improvement by accelerometry and 45% Improvement in CRS compared to baseline
Botulinum toxin A in the treatment of essential tremor						
Botulinum toxin A (hand tremor)	C	6	206	50–100 U/arm	Moderate (hand and finger weakness, reduced grip strength, pain at injection site, stiffness, cramping, hematoma, paresthesias)	20% Improvement in CRS for low and high-dose BTX for postural tremor at 6, 12, and 16 weeks, and 27% improvement in kinetic tremor at 6 weeks (only significant scores listed)
Botulinum toxin A (head tremor)	C	3	53	40–400 U	Mild-moderate (neck weakness, post-injection pain)	67% Improvement by accelerometry, Moderate to Marked improvement by CRS, but did not differ from placebo
Botulinum toxin A (voice tremor)	C	3	25	0.6–15 U	Mild-moderate (breathiness, weak voice, swallowing difficulty)	22% Improvement with unilateral injection, 30% with bilateral injection, 67% Improvement in self-report

* Adverse events severity: mild = somewhat bothersome; moderate = very bothersome; severe = potentially harmful to patients.

CRS = Clinical Rating Scale.

propranolol LA provides effective tremor suppression in ET. In these studies, propranolol LA provided the same therapeutic response as conventional propranolol. Eighty-seven percent of patients in one study preferred propranolol LA to propranolol for ease of administration.[14]

Primidone (Mysoline). Primidone is an anticonvulsant that is metabolized to phenylethylmalonamide (PEMA) and phenobarbital. There were 12 articles that examined the efficacy of primidone in treating ET (n = 218). Four class I studies found that primidone effectively reduced limb tremor in ET, using doses from 50 to 1,000 mg/day. Only three studies provided mean doses of primidone, which averaged 481.7 mg/day. The mean reduction in tremor magnitude by accelerometry was approximately 50%. Primidone was associated with a moderate to high frequency of adverse events that were more se-

Table 2 *Nonpharmacologic agents in the treatment of essential tremor*

Drug	Level of evidence	No. of studies	Cohort size	Adverse events severity*	Magnitude of effect
Chronic thalamic DBS (hand)	C	24	398	Mild to severe (dysarthria, dysequilibrium, paresthesias, weakness, headache, intracranial hemorrhage, subdural hemorrhage, lead dislodgement, ischemic changes, generalized motor seizures, decreased verbal fluency)	60% to 90% Improvement in CRS
Thalamotomy	C	8	181	Mild to severe (hemiparesis, transient problems with speech and motor function, dysarthria, verbal or cognitive deficit, weakness, confusion, somnolence, facial paresis)	55% to 90% Improvement in tremor by CRS
Gamma knife surgery	U	2	61	Mild to severe (transient arm weakness, numbness in the contralateral arm, dysarthria, increased action tremor, dystonia of the contralateral upper and lower limbs, choreoathetosis); case report documented delayed side effects	70% to 85% Improvement in CRS
Chronic thalamic DBS (head)	U	3	72	Mild to severe (dysarthria, dysequilibrium, paresthesias, weakness, headache, weakness, intracranial hemorrhage, subdural hemorrhage, microthalamotomy effect, lead dislodgement, ischemic changes, generalized motor seizures, decreased verbal fluency)	N/A
Chronic thalamic DBS (voice)	U	1	7	Mild to severe (dysarthria, dysequilibrium, paresthesias, weakness, headache, weakness, intracranial hemorrhage, subdural hemorrhage, microthalamotomy effect, lead dislodgement, ischemic changes, generalized motor seizures, decreased verbal fluency)	N/A
Unilateral vs bilateral DBS (hand)	U	1	13	More frequent side effects with bilateral surgery	N/A

* Adverse events severity: mild = somewhat bothersome; moderate = very bothersome; severe = potentially harmful to patients.

DBS = deep brain stimulation; CRS = Clinical Rating Scale.

vere at treatment initiation. These included sedation, drowsiness, fatigue, nausea, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, and an acute toxic reaction. One class I study (n = 40) found that the use of a very low initial dose of primidone (7.5 mg/day) and slow titration (increasing by 7.5 mg/day for 20 days) did not improve primidone tolerability.[15] One class III study (n = 113) evaluated the use of primidone at low doses (250 mg/day) compared to high doses (750 mg/day) in a double-blind study using a clinical rating scale,[16] and there were no significant differences in tremor evaluations between the two groups.

Conclusions. Prospective, randomized clinical trials indicate that propranolol, propranolol LA, and primidone reduce limb tremor in ET. Magnitudes of effect of primidone and propranolol were approximately similar. Limited data indicate that propranolol LA is as effective as standard propranolol for reducing tremor.

Recommendations. Propranolol, propranolol LA, or primidone should be offered to patients who desire treatment for limb tremor in ET, depending on concurrent medical conditions and potential side effects (Level A).

1Ai. Which drug should be used for initial treatment of ET? Three studies compared the initial efficacy of primidone and propranolol in reducing ET. One prospective, double-blind, randomized, placebo-controlled crossover study compared the effects of propranolol (maximum dose 40 mg three times a day), primidone (maximum dose 250 mg three times a day), and placebo in 14 patients with ET.[17] Both propranolol ($p < 0.01$) and primidone ($p < 0.01$) significantly reduced limb tremor from baseline and as compared to placebo. Nine of the 14 patients preferred primidone to propranolol, but primidone caused more bothersome side effects including malaise, dizziness, and unsteadiness at the initial dose of 62.5 mg/day (class II). Another 4-week prospective, patient-blinded, placebo-controlled study in 13 patients with ET compared the effects of placebo, propranolol 20 mg three times a day, and primidone 250 mg three times a day.[18] Both primidone and propranolol significantly reduced tremor, whereas placebo had no effect. There was equivalent reduction in tremor magnitude after 1 week of propranolol treatment and 2 weeks of primidone treatment (class III).

The acute and chronic effects of propranolol and primidone for the treatment of ET were also examined in a 1-year, randomized, open label trial.[7] Twenty-five patients received long-acting propranolol, starting with 80 mg/day and increasing to 160

mg/day as necessary. Twenty-five patients received primidone 50 mg at night, increasing to 250 mg at night as necessary. Patients were evaluated at 3-month intervals using self-evaluation forms, writing samples, a clinical tremor scale, and accelerometry. Propranolol had no measurable benefit in 7 of 23 patients (30%). Four additional patients discontinued the drug due to side effects including fatigue, impotence, and bradycardia. Primidone was without benefit in 7 of 22 (32%) patients. Transient acute side effects occurred in eight patients taking primidone and included nausea, ataxia, dizziness, sedation, and confusion. The investigators concluded that propranolol and primidone are efficacious long-term treatments for some patients with ET, but acute adverse reactions with primidone and chronic side effects with propranolol limit effectiveness (class III).

Conclusions. Primidone and propranolol have similar efficacy when used as initial therapy to treat limb tremor in ET.

Recommendations. Either primidone or propranolol may be used as initial therapy to treat limb tremor in ET (Level B).

1B. Pharmacologic agents with Level B recommendation. *Alprazolam (Xanax).* Alprazolam is a short-acting benzodiazepine. One class I study[19] and one class II study[20] that used clinical rating scales found that alprazolam reduced limb tremor (25% to 34% improvement in clinical ratings compared to placebo) in doses of 0.125 to 3 mg/day. Side effects ranged from none to 50% in these studies and included mild sedation and fatigue. Alprazolam is probably efficacious in treating ET, but its use is recommended with caution due to its abuse potential.[21]

Atenolol (Tenormin). Atenolol is a selective beta-1-adrenoreceptor antagonist with low lipid solubility. Limited data indicate that atenolol has anti-tremor efficacy in patients with ET. However, in one study, atenolol had a lower magnitude of effect than sotalol and propranolol.[22] Doses of atenolol ranged from 50 to 150 mg/day. Adverse events were mild and consisted of lightheadedness, nausea, cough, dry mouth, and sleepiness.

Gabapentin (Neurontin) (monotherapy). Gabapentin is an anticonvulsant with a structure similar to gamma-aminobutyric acid (GABA) and is approved as adjunctive therapy for partial seizures. One class I study found that gabapentin reduced tremor when used as monotherapy in doses of 1,200 mg/day (n = 16), with a 77% improvement in tremor as measured by accelerometry at day 15.[23]

Sotalol (Sotacor). Sotalol is a nonselective beta-adrenergic receptor antagonist. In one study, sotalol effectively reduced tremor compared to placebo as measured by both subjective and objective assessments[24] (class I).

Topiramate (Topamax). Topiramate is an anticonvulsant that blocks sodium channels and potentiates GABA activity. Three class II studies[25-27] and one class IV study[28] found that topiramate in doses up to 400 mg/day reduced tremor. One double-blind, placebo-controlled trial[28] in 62 patients with ET reported an 18% to 23% improvement in clinical rating scales with topiramate use, compared to 0 to 1% in patients taking placebo. The drop-out rate was approximately 40% due to appetite suppression, weight loss, paresthesias, anorexia, and concentration difficulties.

Propranolol (head tremor). One class I study of 18 patients with ET demonstrated that propranolol reduced head tremor amplitude by about 50% as measured by accelerometry.[29] Conversely, one class II (n = 9)[30] and one class III study (n = 9)[31] failed to find reduction in head tremor using propranolol.

Conclusions. Alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate probably reduce limb tremor associated with ET. Propranolol probably reduces head tremor in ET, but data are limited.

Recommendations. Atenolol, gabapentin (monotherapy), sotalol, and topiramate should be considered as treatment of limb tremor associated with ET (Level B). Alprazolam is recommended with caution due to its abuse potential (Level B). Propranolol should be considered as treatment of head tremor in patients with ET (Level B).

1C. Pharmacologic agents with Level C recommendation. *Clonazepam (Klonopin).* Clonazepam, a benzodiazepine, significantly reduced kinetic tremor in 14 patients in one class II study using doses ranging from 0.5 to 6 mg/day.[32] Clonazepam had little efficacy in a class III study of 15 patients taking 0.5 to 4 mg/day, and there was a 40% completion rate due to drowsiness.[33] The use of clonazepam is recommended with caution due to its abuse potential and possible withdrawal symptoms following abrupt discontinuance.[34]

Clozapine (Clozaril). Clozapine is an atypical neuroleptic with minimal extrapyramidal side effects. Two studies found that clozapine reduced ET in doses of 6 to 75 mg/day.[35,36] In one class II study, 87% of patients had at least a 50% reduction in tremor as measured by clinical tremor rating scales,[35] and there was approximately a 45% reduction in tremor amplitude as measured by accelerometry acutely.[36] Sedation decreased "markedly" after 6 to 7 weeks in 12 of 13 patients in this study. None of the patients in either study experienced agranulocytosis.

Nadolol (Corgard). Nadolol is a beta-adrenergic receptor blocking agent and an antihypertensive agent. One class II study in 10 patients with ET found that nadolol, in doses of 120 or 240 mg/day, reduced tremor in a double-blind, placebo-controlled trial using accelerometry.[37] However, only patients who had previously responded to propranolol experienced significant tremor reduction from nadolol. There were no statistical differences between the groups taking either dose, and no adverse reactions were reported.

Nimodipine (Nimotop). Nimodipine, a calcium channel blocker, at a dose of 30 mg four times daily

reduced tremor amplitude by 53% as measured by accelerometry in one class I study (n = 16).[38] Fifteen of 16 patients completed the study, and eight patients improved.

Conclusions. Clonazepam, clozapine, nadolol, and nimodipine possibly reduce limb tremor associated with ET.

Recommendations. Nadolol and nimodipine may be considered when treating limb tremor in patients with ET (Level C). Clonazepam should be used with caution due to its abuse potential and possible withdrawal symptoms (Level C). Clozapine is recommended only for refractory cases of limb tremor in ET due to the risk of agranulocytosis (Level C).

1D. Pharmacologic agents with recommendations against use (Level A). *Trazodone (Desyrel).* Two class I studies (n = 24) found that trazodone, a serotoninergic agonist, did not significantly alter postural or kinetic tremor as measured by clinical scores.[39,40]

Conclusions. Trazodone is ineffective in reducing limb tremor associated with ET.

Recommendations. Trazodone is not recommended for treatment of limb tremor in ET (Level A).

1E. Pharmacologic agents with recommendations against use (Level B). *Acetazolamide (Diamox).* Acetazolamide is a carbonic anhydrase inhibitor. One class I study evaluated the efficacy of acetazolamide in reducing ET compared to placebo (n = 19).[19] Acetazolamide in doses ranging from 62.5 to 750 mg/day use did not result in significant tremor reduction. Another class IV, open-label study found that acetazolamide (in doses up to 500 mg/day) reduced tremor severity, but did not improve patient self-assessment or motor task scale.[41]

Isoniazid (Laniazid, Nydrazid). Isoniazid is an antibacterial agent that is used to treat tuberculosis. One class II study randomized 11 patients with ET to isoniazid (doses up to 1,200 mg/day) or placebo over a 4-week period.[42] Only 2 of 11 patients had objective or subjective response to isoniazid.

Pindolol (Visken). Pindolol is a beta-blocker and an antihypertensive agent. One class I study found that pindolol 15 mg/day (n = 24) did not reduce tremor amplitude or frequency compared to baseline as measured by accelerometry.[43]

Conclusions. Acetazolamide, isoniazid, and pindolol probably do not reduce limb tremor associated with ET.

Recommendations. Acetazolamide, isoniazid, and pindolol are not recommended for treatment of limb tremor in ET (Level B).

1F. Pharmacologic agents with recommendations against use (Level C). *Methazolamide (Neptazane).* Methazolamide is a carbonic anhydrase inhibitor that is used to treat ocular conditions such as glaucoma.[44] One class II study evaluating the use of methazolamide in doses of 50 to 300 mg/day did not find a reduction in tremor compared to placebo using patient self-assessment, tremor severity scales, and accelerometry.[45]

Mirtazapine (Remeron). Mirtazapine is an antidepressant that acts as an α-2-receptor antagonist and selective blocker of postsynaptic 5HT2 and 5HT3 receptors.[46] One class II study evaluated the safety and tolerability of mirtazapine in 17 patients with ET and found no significant improvement with mirtazapine use.[47]

Nifedipine (Adalat, Procardia). Nifedipine is a calcium channel blocker and an antihypertensive. One class II study found that nifedipine 10 mg/day as a single dose increased tremor by 71% as measured by accelerometry.[48]

Verapamil (Calan). Verapamil is an antihypertensive agent that acts as a calcium ion influx inhibitor. One class II study found that a single 80 mg dose of verapamil taken orally did not alter tremor activity in patients with ET.[48]

Conclusions. Methazolamide, mirtazapine, nifedipine, and verapamil probably do not reduce limb tremor in ET.

Recommendations. Methazolamide, mirtazapine, nifedipine, and verapamil are not recommended for treatment of limb tremor in ET (Level C).

1G. Pharmacologic agents with level U recommendation. There are several additional drugs listed in table 1 that may reduce tremor. However, the studies were too small to make a recommendation, or the results were conflicting, resulting in a Level U recommendation.

Amantadine (Symmetrel). Amantadine is an antiviral and antiparkinsonian agent. One class III study found that amantadine 100 mg twice daily given to six patients with ET for a 1-month period did not reduce tremor amplitude or frequency.[49]

Clonidine (Catapres). Clonidine is an α_2-adrenergic agonist that is used as an antihypertensive agent. Two class II studies[50,51] found that clonidine effectively reduced tremor magnitude in patients with ET, although one class II study found that tremor was not significantly altered by clonidine therapy.[52]

Gabapentin (Neurontin) (adjunct therapy). Two class II studies (n = 45)[53,54] reported little or modest benefit when gabapentin was used as adjunctive therapy in doses of 1,800 and 3,600 mg/day. One study found no significant changes in clinical rating scale scores,[54] while the other study found a 42% improvement from gabapentin and a 28% improvement from placebo.[53] There was a 12% reduction in tremor with gabapentin by accelerometry, but this was not significant.[53]

Glutethimide (Doriden). Glutethimide is a nonbarbiturate sedative agent that reduced ET by class IV data only.[55]

L-Tryptophan/Pyridoxine. L-Tryptophan is an amino acid precursor of tryptamine and serotonin, and pyridoxine is a coenzyme for dopa decarboxylase. One case series demonstrated that l-tryptophan/pyridoxine failed to improve tremor in 2 patients with ET.[56]

Metoprolol (Lopressor, Toprol). Metoprolol is a beta-1-adrenoreceptor antagonist, and the evidence regarding its anti-tremor efficacy is conflicting. One class I study showed that a single dose of 150 mg metoprolol improved tremor.[57] However, one class I study found that metoprolol was ineffective for the management of limb tremor in ET when used in doses of 150 and 300 mg/day for 2 to 4 weeks.[58]

Nicardipine (Cardene). Nicardipine is a calcium channel blocker and an antihypertensive agent. One class II study found that nicardipine over a 4-week period did not reduce tremor significantly, while a single 30 mg dose produced significant reductions in tremor amplitude compared to baseline and placebo.[59]

Olanzapine (Zyprexa). The atypical antipsychotic medication olanzapine reduced tremor in a class IV study using a mean dose of 14.87 mg/day.[60] Twenty percent of patients reported sedation, and several patients reported weight gain.

Phenobarbital (Luminal). Phenobarbital is an anticonvulsant and a sedative. One class II study (n = 17) that evaluated the anti-tremor effect of phenobarbital compared to propranolol and placebo found that while phenobarbital was better than placebo when tremor was measured with accelerometry but not with a clinical rating scale.[61] Another class I study (n = 16) found that phenobarbital (mean dose 136 ± 25 mg/day) was no better than placebo.[62]

Quetiapine (Seroquel). Quetiapine is an atypical antipsychotic agent. One class IV study (n = 10) evaluated the safety and tolerability of quetiapine (up to 75 mg/day) as monotherapy in ET over a 6-week period.[63] Patients were evaluated with a clinical rating scale. Six patients completed the study, and the mean tolerated dose of quetiapine was 60 mg ± 21.08 (range 25 to 75 mg). The most common side effect was somnolence. No statistical differences were noted pre- and post-treatment.

Theophylline (Theo-dur). Theophylline is a xanthine derivative bronchodilator that can induce tremor.[64,65] However, several studies have demonstrated that theophylline in low doses may improve ET.[66,67] In one double-blind, crossover study, patients who were given a single oral dose of theophylline had no significant change in tremor for the following 24 hours.[66] However, tremor was significantly improved after 4 weeks of treatment with theophylline 300 mg/day as measured by clinical rating scales. In another double-blind trial, patients were given placebo, propranolol 80 mg/day, or theophylline 150 mg/day for 4 weeks.[67] No reduction in tremor was noted in patients taking theophylline until the end of the second week of treatment. Both propranolol and theophylline reduced tremor at study endpoint compared to baseline. No adverse events were reported with theophylline use.

Conclusions. There are insufficient or conflicting data regarding the use of amantadine, clonidine, gabapentin (adjunct therapy), glutethimide, L-tryptophan/pyridoxine, metoprolol, nicardipine, olanzapine, phenobarbital, quetiapine, and theophylline to treat limb tremor associated with ET.

Recommendations. There is insufficient evidence to make recommendations regarding the use of amantadine, clonidine, gabapentin (adjunct therapy), glutethimide, L-tryptophan/pyridoxine, metoprolol, nicardipine, olanzapine, phenobarbital, quetiapine, and theophylline in the treatment of limb tremor in ET (Level U).

2. In patients with ET, is combined treatment with primidone and propranolol superior to monotherapy? Several studies have addressed this question, but none employed double-blind, randomized methodology. One study (class II) found that the addition of primidone 50 to 1,000 mg/day to propranolol reduced tremor amplitude more than when propranolol was used alone.[68] Propranolol monotherapy at the maximum effective dose (average dose 260 mg/day) reduced tremor amplitude a mean of 35%, while the addition of primidone (50 to 1,000 mg/day) decreased tremor by a mean of 60 to 70%. Twelve percent of patients had acute reactions to primidone administration including ataxia and confusion. Titration was limited in nine patients due to sedation and vertigo. In another study, 18 patients received in random order placebo, primidone (250 mg/day), propranolol (240 mg/day), both drugs, or no drugs (class II). Accelerometric recordings were made of both postural and kinetic tremor. Primidone and propranolol alone were equally efficacious in treating both postural and kinetic tremor. The combined use of primidone and propranolol was more effective than either drug alone for both types of tremor ($p < 0.05$), although the magnitude of this effect was small.[5]

Conclusions. The combined use of primidone and propranolol possibly reduces limb tremor in ET more than either drug alone. There was no worsening of adverse events when primidone and propranolol were used in combination.

Recommendations. Primidone and propranolol may be used in combination to treat limb tremor when monotherapy does not sufficiently reduce tremor (Level B).

3. In patients with ET, is there evidence for sustained benefit of pharmacologic treatment? One trial found that primidone (doses 375 to 750 mg/day) was effective for up to 1 year[69] (class III). In another open label extension study, 18 patients with ET took propranolol for 12 months.[70] Propranolol continued to provide benefit although 5 of 12 patients (42%) required an increased dose at 12 months compared to 3 to 6 months. Eighty-three percent of patients experienced greater than 20% reduction in tremor after 3 to 6 months (using clinical tests such as handwriting and drawing, self-rating of functional disability, and accelerometry) while 66% of patients had their tremor magnitude reduced by more than 20% of their baseline values after 12 months (class III). A third open-label study examined the acute and chronic effects of propranolol and primidone in 50 patients with ET who were randomly assigned to receive either long-acting propranolol (80 to 160 mg/day) or primidone (50 to 250 mg/day).[7] Patients were

evaluated at 1, 3, 6, 9, and 12 months of treatment, and tremor was assessed by rating scales and accelerometry. Ten of 25 patients (40%) treated with propranolol continued to benefit after 1 year of treatment. In four patients, the dose of propranolol remained the same, while in the other six patients, the dose was increased. At the end of 1 year, propranolol controlled symptoms in 40% of patients with the majority requiring an increase in dosage. Over 50% of patients who were treated with primidone maintained benefit at 1 year. Reduction in clinical benefit occurred in 12.5% of patients treated with propranolol and 13.0% of those taking primidone (class III). Another double-blind study found that both low doses of primidone (250 mg/day) and high doses of primidone (750 mg/day) improved ET for 12 months (class II).[16]

Conclusions. Primidone and propranolol maintain anti-tremor efficacy in the majority of patients for at least 1 year.

Recommendations. The dosages of propranolol and primidone may need to be increased by 12 months of therapy when treating limb tremor in ET (Level C).

4. Do patients with ET benefit from chemodenervation with botulinum toxin type A or B? Botulinum toxin (BTX) A has been used to treat hand, head, and voice tremor in ET. Twelve studies evaluated the safety and effectiveness of BTX A in treating ET (6 for limb tremor [n = 210], 3 for head tremor [n = 62], and 3 for voice tremor [n = 25]), while there are no studies that evaluated the use of BTX B to treat ET. One class I study randomized 133 patients with ET to receive injections of 50 U or 100 U of BTX into their limbs and demonstrated modest benefit.[71] For those patients who received a total of 50 U of BTX, 15 U were injected into each of the flexor carpi radialis and ulnaris and 10 U into each of the extensor carpi radialis and ulnaris. For those patients who received a total of 100 U of BTX, 30 U were injected into each of the flexor carpi radialis and ulnaris and 20 U into each of the extensor carpi radialis and ulnaris. Clinical tremor rating scale scores significantly improved from baseline for the low- and high-dose groups for postural tremor at 6, 12, and 16 weeks and for kinetic tremor at the 6-week evaluation. Subjective assessments indicated mild improvement for low and high dose groups at 6 weeks, but no change at 12 and 16 weeks. The magnitude of the change in postural tremor was on average less than one point on the rating scale, and kinetic tremor was only reduced at the 6-week evaluation. There was minimal functional improvement, and neither physician nor patient reported any benefit at 12- and 16-week follow-up. Hand weakness was reported in 30% of patients in the low-dose group and in 70% of patients in the high-dose group. Additional side effects included pain at the injection site, stiffness, cramping, hematoma, and paresthesias. These side effects made blinded treatment and evaluation difficult, if not impossible.

One class II study that evaluated the use of BTX A to treat head tremor in 10 patients with ET found that there was moderate to marked improvement in clinical rating scales in five patients with BTX injections and in one patient with placebo injections.[72] Forty units of BTX were injected into each sternocleidomastoid muscle, and 60 U were injected into each splenius capitis muscle using EMG guidance. Five patients had moderate to marked improvements in subjective ratings scales, compared to three patients who received placebo. However, subjective and clinical rating scale evaluations did not differ significantly between those who received BTX and those who received placebo. Side effects consisted of neck weakness and post-injection pain in most patients. Another open-label study using clinical rating scales and accelerometry found that tremor amplitude changed significantly after BTX injections compared to baseline (baseline 0.079, post-treatment 0.0255, $p < 0.05$), and all patients reported subjective improvement.[73]

Two class III studies using blinded voice analysis evaluated the effects of BTX A on voice tremor.[74,75] In one study, 30% of patients (3 of 10) demonstrated an objective reduction in tremor severity with bilateral injection into the vocal cords, compared to 22% of those who received unilateral injection.[74] Another study (n = 15) found a 67% self-report of benefit following BTX injections.[75] Eighty percent of patients reported breathy, weak voices for 1 to 2 weeks, while 20% had hoarseness and swallowing difficulties for 4 weeks.

Conclusions. The effect of BTX A on limb tremor in ET is modest and is associated with dose-dependent hand weakness. BTX A may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, BTX A may cause breathiness, hoarseness, and swallowing difficulties.

Recommendations. BTX A injections for limb, head, and voice tremor associated with ET may be considered in medically refractory cases (Level C for limb, head, and voice tremor).

Analysis of the evidence: Surgical treatment of ET. *5. What is the efficacy of thalamotomy in treating contralateral limb tremor in patients with ET?* Thalamotomy involves creating a lesion in the ventral intermediate nucleus (VIM) of the thalamus. The area is localized using stereotactic techniques, and the location can be confirmed by macro-stimulation (assessing the clinical effects of high frequency stimulation to see if the tremor will improve without unwanted effects) and micro-electrode recording techniques (measuring the electrical activity of individual neurons to ensure that their discharge pattern is typical for the desired target).

Open label trials (n = 181) indicate that thalamotomy reduces limb tremor in 80 to 90% of patients with ET. One class I study found that tremor was abolished "completely" or "almost completely" in 79% of patients.[76] A class III study found that tremor was abolished in 90% of patients who received thalamot-

omies,[77] while another class III study reported that there was an 83% improvement in action tremor, a 77% improvement in postural tremor, and a 56% improvement in handwriting and drawing 3 months after surgery.[78] In all studies, most patients experienced either complete abolition of tremor or marked to moderate improvement, and studies indicate that there is long-term benefit from the procedure. Prospective comparisons against best medical management are lacking, although thalamotomy is reserved for medically refractory patients. Adverse events associated with thalamotomy occurred in 14 to 47% of patients. Twenty-nine patients in all of the examined studies had adverse effects that did not resolve with time (16%). In one study (n = 37), 16% of patients who underwent a unilateral thalamotomy had permanent hemiparesis and speech difficulty.[79] Other adverse events include transient problems with speech and motor function, dysarthria, verbal or cognitive deficit, weakness, confusion, somnolence, and facial paresis.

Limited data indicate that bilateral thalamotomy is associated with a high frequency of side effects, although most of these studies focused on bilateral thalamotomy in PD rather than in ET.[80-84] Dysarthria, dysphonia, and voice reduction has been reported in 28 to 88% of patients with PD who received bilateral thalamotomies[80,84] and the condition was marked in 67% of patients.[84] Additionally, 64% of patients with PD in one study reported transient mental confusion,[80] and 54% of patients with PD in another study[84] reported mental changes. Bilateral thalamotomy is no longer performed to treat ET.

Conclusions. Unilateral thalamotomy effectively treats contralateral limb tremor in ET. Bilateral thalamotomy is associated with more frequent and often severe side effects.

Recommendations. Unilateral thalamotomy may be used to treat limb tremor in ET that is refractory to medical management (Level C), but bilateral thalamotomy is not recommended due to adverse side effects (Level C).

6. What is the efficacy of deep brain stimulation of the thalamus in treating tremor in patients with refractory ET? 6A. Deep brain stimulation (unilateral and bilateral) and limb tremor. Deep brain stimulation (DBS) uses high frequency electrical stimulation from an implanted electrode to modify the activity of the target area. The exact mechanisms by which DBS suppresses tremor are unknown, and postmortem examinations have not shown any permanent anatomic changes other than the electrode tract.[85,86] Placement strategies are similar to those for thalamotomy. For ET, the electrode is inserted into the VIM thalamus. It is connected to a pulse generator that is placed in the chest wall. Electrode montage (four electrodes placed 1.5 mm apart and the electrode case), voltage, pulse frequency, and pulse width can be adjusted to optimize tremor control.[87] This flexibility in placing and adjusting the "functional lesion" is the main advantage of DBS compared to thalamotomy. Potential disadvantages include the greater cost and effort in programming and maintaining the device.

Ethical and cost considerations are often stated to preclude ideal controlled study designs that would necessarily include "sham" surgeries, or in the case of DBS, implanting nonfunctioning devices. However, DBS is uniquely suited to single blind evaluations since it can be easily activated and inactivated prior to assessment by a blinded investigator. Electrophysiologic measures including accelerometry have also been used in several studies for tremor assessment.

Studies indicate that contralateral limb tremor is consistently improved by DBS, as determined by observation, writing tests, pouring tests, and activities of daily living questionnaires (n = 82 patients). Two prospective, blinded trials have examined the effects of DBS in patients with ET (n = 23)[88,89] (class III). Although the treatment of patients was not randomized, evaluation was conducted in a blinded, random manner. Following unilateral DBS, there was a mean tremor improvement of 60% to 90% on clinical rating scales. Results of the few trials with both blinded (to activation status) and unblinded postsurgical evaluations on the same patients demonstrate there was negligible "placebo response" and significant tremor reduction.

Bilateral thalamic stimulation was evaluated in nine medically refractory patients with ET at baseline before the first implant, before the second implant, and at 6 and 12 months following surgeries.[89] Motor scores when the implant was "off" did not differ between baseline evaluations and those performed 6 and 12 months after surgery. However, there were significant improvements in motor scores when the implant was activated at both the 6- and 12-month evaluations (class III). For postural and kinetic tremor, there was a 67% improvement in hand tremor on the first side and a 64% improvement on the second side following surgery. The mean total tremor score improved from 66.1 ± 11.6 to 28.4 ± 12.8 12 months after the second surgery ($p < 0.05$).

In all studies, a total of 37 patients experienced adverse effects resulting from DBS (18%). Of these, 28 were related to equipment malfunction or lead displacement. One study reported a death associated with the procedure due to a perioperative intracerebral hemorrhage.[76] Other side effects associated with DBS were dysarthria, dysequilibrium, paresthesias, weakness, headache, intracranial hemorrhage, subdural hemorrhage, lead dislodgement, ischemic changes, generalized motor seizures, and decreased verbal fluency. Many of these side effects resolved with time or with adjustment of stimulator settings.

Conclusions. DBS of the VIM thalamic nucleus effectively reduces contralateral limb tremor in medically refractory ET.

Recommendations. DBS of the VIM thalamic nucleus may be used to treat medically refractory limb

tremor in ET (Level C).6B. DBS and head and voice tremor. Data on the reduction of voice tremor after DBS is limited. One class III study found that DBS effectively reduced voice tremor in seven patients with ET (five unilateral, two bilateral).[90] All patients had undergone DBS for management of upper limb tremor. Four of seven patients had voice tremor reduction as measured by objective tests. The patient who had the greatest improvement in voice tremor had received bilateral implantation, although another patient who received bilateral stimulation had no appreciable reduction in voice tremor. Another open-label study of patients with PD, ET, and MS who received bilateral thalamic stimulation found that six of seven patients with voice tremor improved one grade on a clinical rating scale.[91] However, an open-label trial failed to find any significant change in voice tremor with unilateral or bilateral thalamic stimulation.[92]

Studies of DBS and head tremor have produced conflicting results. One class III study that evaluated the effect of unilateral thalamic DBS on head tremor failed to find an improvement.[93] Another class III study of 38 patients found that unilateral DBS of the thalamus improved head tremor in 71% of patients at 3-month postoperative evaluation, while 26% of patients were unchanged and 3% worsened.[94] An open-label study (class IV, n = 15) also reported that 90% of patients with ET experienced improvement in head tremor after bilateral DBS.[91] In all studies, adverse events were similar to those of DBS for limb tremor.

Conclusions. There are conflicting data regarding the use of DBS for head and voice tremor in ET.

Recommendations. There is insufficient evidence to make recommendations regarding the use of thalamic DBS for head or voice tremor (Level U).

7. Should thalamotomy or DBS of the thalamus be the procedure of choice in patients with medically refractory ET? In a class I study, 13 patients with ET were randomly assigned to undergo either thalamotomy or DBS, and functional abilities were compared preoperatively and 6 months postoperatively using the Frenchay Activities Index (FAI).[76] Functional ratings improved more in patients who received thalamic stimulation than in those who received thalamotomy. Side effects were present in 50% of thalamotomy patients and included cognitive deterioration, mild dysarthria, and mild gait or balance disturbance. In the DBS group, one patient (14% of treated patients) had mild gait and balance disturbance. The authors concluded that while both DBS and thalamotomy effectively reduced tremor, DBS has fewer adverse effects and resulted in greater functional improvement.

In another open-label study, 17 patients with ET received thalamotomy and were matched to 17 patients with ET who had previously received DBS.[95] There were no significant differences between any efficacy outcome variables comparing thalamotomy to DBS of the thalamus at baseline or follow-up visits. However, surgical complications were higher for the patients who received thalamotomy compared to DBS. Five patients who received thalamotomy had asymptomatic intracranial hemorrhages, and one patient had a symptomatic hemorrhage. Five patients reported cognitive abnormalities, two patients experienced hemiparesis, and two patients had aphasia. All complications resolved within 1 month. Complications of DBS included seizures in one patient, although four patients eventually had a lead replaced, one had IPG malfunction, and one had surgery for a dead battery. The authors concluded that DBS should be the procedure of choice due to fewer serious adverse events (class IV). A similar class IV retrospective study of six patients with ET found no difference in the clinical benefit achieved by either procedure.[96] However, ataxia, dysarthria, and gait disturbance were more common after thalamotomy (42%) than DBS (26%). Both PD and ET patients were included in this study (class IV).

Conclusions. Both DBS and thalamotomy effectively suppress tremor in ET.

Recommendations. DBS has fewer adverse events than thalamotomy (Level B). However, the decision to use either procedure depends on each patient's circumstances and risk for intraoperative complications compared to feasibility of stimulator monitoring and adjustments.

8. What are the indications for bilateral vs unilateral surgical procedures in ET? One class III study comparatively examined the effects of unilateral vs bilateral DBS.[97] This study of 13 patients with ET found that bilateral thalamic DBS was more effective than unilateral DBS at controlling appendicular and midline tremors. Using the Unified Tremor Rating Scale, hand tremor scores in patients with ET randomized to "on" stimulation improved from 6.7 ± 0.9 to 1.3 ± 1.2 ($p < 0.005$) at the 3-month, second side assessment, and legs improved from 2.3 ± 1.1 to 0.5 ± 0.5 ($p < 0.005$). Side effects, including dysarthria, tended to occur more frequently in patients who underwent bilateral DBS.

In another study, bilateral thalamic stimulation was performed in nine medically refractory patients with ET.[89] Patients received evaluations at baseline, before the first implant, before the second implant, and at 6 and 12 months following surgeries. Tremor scores tended to be better following the second procedure than after the first procedure (class III). Speech evaluations were available for six of the nine patients, and three of the six patients had worsening of dysarthria with both stimulators on.

Conclusions. Thalamic DBS suppresses contralateral limb tremor, so bilateral DBS is necessary to suppress tremor in both upper limbs. However, there is no evidence of a synergistic effect on limb tremor with bilateral DBS, and there are insufficient data regarding the risk:benefit ratios of unilateral vs bilateral DBS. Similarly, there are insufficient data regarding the use of bilateral DBS for head and voice tremors.

Recommendations. Bilateral DBS is necessary to suppress tremor in both upper limbs, but there are insufficient data regarding the risk:benefit ratio of bilateral vs unilateral DBS in the treatment of limb tremor (Level U). Similarly, there are insufficient data to recommend bilateral or unilateral DBS for head and voice tremors. Side effects are more frequent with bilateral DBS, and bilateral thalamotomy is not recommended.

9. Does gamma knife thalamotomy effectively reduce ET? Gamma knife surgery is performed by delivering radiation to an intracranial target based on anatomic imaging. Electrophysiologic guidance is not possible. Several studies (n = 61) have reported favorable results with gamma knife thalamotomy,[98,99] although one case report documented delayed side effects from the procedure including contralateral arm numbness and dysarthria.[100] In one retrospective study (class IV), gamma knife treatment resulted in complete tremor arrest in 75% of patients (n = 9), and all patients benefited subjectively from the procedure.[98] There were significant improvements in drawing capability at follow-up (median of 6 months). The onset of improvement occurred at a median of 6 weeks following the procedure, and additional improvements continued for the next 6 months. One patient developed transient arm weakness. In a class III study, 52 patients with ET received unilateral gamma knife thalamotomy and were followed for a median of 26 months.[99] Patients were assessed using the Fahn-Tolosa-Marin rating scale with blinded assessments. At 1 year after surgery, 92% of patients were completely or nearly completely free of tremor; at 4-year follow-up, this percentage decreased to 88%. One patient experienced mild contralateral arm and leg weakness, while another patient developed transient paresthesias. However, one case report (class IV) described severe complications that occurred approximately 7 months after gamma knife thalamotomy.[100] These complications were progressive and included numbness in the contralateral arm, dysarthria, increased action tremor, dystonia of the contralateral upper and lower limbs, and choreoathetosis. The dependence on anatomic imaging, the typical delay of weeks to months for clinical results to occur, and the risks of delayed progressive neurologic deficits are disadvantages of gamma knife thalamotomy, compared to thalamic DBS. Long-term follow-up studies are needed to assess the risk:benefit ratio of gamma knife thalamotomy.

Conclusions. Several studies have found favorable results with gamma knife thalamotomy, but delayed complications have been reported, and clinical improvement may take weeks to months to occur.

Recommendations. There is insufficient evidence to make recommendations regarding the use of gamma knife thalamotomy in the treatment of ET (Level U).

Future research recommendations. Despite being one of the most common adult movement disorders, research on treatment of ET is limited. Future research considerations include the following:

1. There should be a concerted effort to standardize outcome measures to assess tremor and to correlate accelerometry with clinical rating scales. This is important in determining the magnitude of effect of pharmacologic or surgical treatments.
2. Knowledge of clinical and pathologic heterogeneity of ET and how these relate to profiles of pharmacologic responsiveness should be determined to help guide clinicians in selecting appropriate medications for their patients.
3. Studies are needed to determine the cost vs benefit profile for treatments of ET.
4. Additional clinical trials should be conducted to assess the pharmacologic and surgical treatment of head and voice tremor.
5. Additional randomized, prospective, double-blind, placebo-controlled trials are needed to better determine the efficacy and side effect profiles of pharmacologic and surgical therapies for ET.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix 1

Classification of evidence

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

a) Primary outcome(s) clearly defined.
b) Exclusion/inclusion criteria clearly defined.
c) Adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias.
d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.

Class III: All other controlled trials including well-defined natural history controls or patients serving as own controls in a representative population, where outcome is independently assessed or independently derived by objective outcome measurement.*

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix 2

Classification of recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)
B = Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)
C = Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U = Data inadequate or conflicting given current knowledge, treatment is unproven.

Appendix 3

Adverse events severity

Mild: Somewhat bothersome but not clinically harmful
Moderate: Very bothersome but not clinically harmful
Severe: Pose/potentially pose harm to patients

Appendix 4

Quality Standards Subcommittee members Gary Franklin, MD, MPH (Co-Chair); Gary Gronseth, MD (Co-Chair); Charles E. Argoff, MD; Stephen Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD; Michael Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; David J. Thurman, MD; Samuel Wiebe, MD; William J. Weiner, MD; and Catherine Zahn, MD (ex-officio).

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T. A. Zesiewicz, R. Elble, E. D. Louis, et al.

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