

Practice Parameter: Therapies for Essential Tremor (An Evidence-Based Review)

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

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Essential Tremor (ET) Epidemiology

- One of the most common tremor disorders in adults
- Population study prevalence estimates range from 0.4%-6%
- Both incidence and prevalence increase with advancing age

Disease Characteristics

- Characterized by kinetic and postural tremor:
 - upper limbs (~95% of patients)
 - head (~34%)
 - lower limbs (~30%)
 - voice (~12%)
 - tongue (~7%)
 - face (~5%)
 - trunk (~5%)
- Criteria for definite and probable ET include:
 - in the absence of other neurological signs abnormal bilateral postural or kinetic tremor of the hands
 - isolated tremor of the head if there is no evidence of dystonia

Disease Characteristics (continued)

- Tremor amplitude increases over time
- Increasing difficulty with fine motor tasks
- Potential physical and psychosocial disability
- Referred to as a “benign” condition
 - doesn’t reduce life expectancy
 - doesn’t cause symptoms besides tremor and gait abnormalities
- Unclear association with co-morbid symptoms

Description of process

- Review of literature
 - Computer assisted literature searches conducted on MEDLINE, EMBASE, Science Citation Index, and CINAHL and limited to:
 - Relevant English language articles pertinent to ET
 - Medications that are available in the United States
 - Between 1966 and 2004

Description of process

- Review of literature (continued)
 - 502 articles were found for treatment and management of ET and were analyzed for content and relevance by individual committee members
 - 211 articles accepted for further review consisted of:
 - double-blind controlled trials
 - open-label studies
 - case series
 - case reports
 - Each further classified by 2 panel members using a four-tiered classification

AAN Strength 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) is/are clearly defined
- b) exclusion/inclusion criteria are 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.

AAN Strength of Evidence

Class III	Class IV
<p>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.</p>	<p>Evidence from uncontrolled studies, case series, case reports, or expert opinion</p>

Translation of Evidence to Recommendation Level

Level A	Level B
<p>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.)</p>	<p>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.)</p>

Translation of Evidence to Recommendation Level

Level C	Level U
<p>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.)</p>	<p>Data inadequate or conflicting given current knowledge, treatment is unproven.</p>

Pharmacologic treatment for ET

- Safety, tolerability, and efficacy of pharmacologic agents in treating ET
- Initial treatment of ET
- Combined treatment with primidone and propranolol vs. monotherapy with either drug alone
- Sustained benefit of pharmacologic treatment

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Primidone	A	12	Mild-moderate	50% CRS and accelerometry
Propranolol	A	32	Mild to moderate	50% CRS and accelerometry
Propranolol LA	A	2	Mild	30-38% accelerometry

Mean improvement by CRS***or accelerometry compared to baseline

*See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients. ***CRS=Clinical Rating Scale

Analysis of Evidence

Intervention	Level of Evidence	# of Studies *	Adverse Events Severity**	Magnitude of Effect
Alprazolam	B	2	Mild	25-34% CRS
Atenolol	B	5	Mild-moderate	25% CRS and 37% accelerometry
Gabapentin Monotherapy	B	3	Mild	33% CRS and 77% accelerometry
Sotalol	B	3	Mild	28% CRS
Topiramate	B	5	Mild	22-37% CRS

Mean improvement by CRS***or accelerometry compared to baseline

*See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients.

***CRS=Clinical Rating Scale

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Clonazepam	C	3	Mild-moderate	26-57% CRS and 71% accelerometry
Clozapine	C	2	Mild-Severe	45% accelerometry

Mean improvement by CRS***or accelerometry compared to baseline
 *See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients. ***CRS=Clinical Rating Scale

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Nadolol	C	1	None	60-70% accelerometry
Nimodipine	C	1	Mild	45% CRS and 53% accelerometry

Mean improvement by CRS***or accelerometry compared to baseline
 *See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients. ***CRS=Clinical Rating Scale

Conclusions

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

Conclusions

- Alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate probably reduce limb tremor associated with ET.
- Propranolol probably reduces head tremor in ET, but data is limited.
- Clonazepam, clozapine, nadolol, and nimodipine possibly reduce limb tremor associated with ET.

Conclusions

Against pharmacologic agents

- Trazodone is ineffective in reducing limb tremor.
- Acetazolamide, isoniazid, and pindolol probably do not reduce limb tremor.
- Methazolamide, mirtazapine, nifedipine, verapamil probably do not reduce limb tremor.
- There is 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.

Analysis of Evidence

Intervention	Class of studies*	Results
Propranolol & Primidone compared to placebo	II	<ul style="list-style-type: none"> • Propranolol ($p < 0.01$) and primidone ($p < 0.01$) reduced limb tremor compared to placebo • Primidone has more side effects at the initial dose of 62.5 mg/day
Placebo, propranolol, and primidone	III	<ul style="list-style-type: none"> • Primidone and propranolol significantly reduced tremor • Placebo had no effect • Equivalent reduction in tremor magnitude after 1 week of propranolol treatment and 2 weeks of primidone treatment

*See full guideline for references.

Analysis of Evidence

Intervention	Class of studies*	Results
Acute and chronic effects of propranolol and primidone	III	<ul style="list-style-type: none"> ● Propranolol: no measurable benefit in 30% pts ● Primidone: w/o benefit in 28% patients ● Propranolol and primidone: effective long-term treatments for some patients ● Acute adverse reactions with primidone and chronic side effects with propranolol limit effectiveness
*See full guideline for references.		

Analysis of Evidence

Intervention	Class of studies*	Results
Primidone and propranolol compared propranolol alone	II	<ul style="list-style-type: none"> • Adding primidone to propranolol reduced tremor more than propranolol alone • Propranolol monotherapy at the max. dose reduced tremor (mean = 35%) • Add primidone decreased tremor (mean = 60-70%)
*See full guideline for references.		

Analysis of Evidence

Intervention	Class of studies*	Results
Placebo, primidone, propranolol, or both drugs	II	<ul style="list-style-type: none">• Primidone and propranolol alone are equally effective in treating postural and kinetic tremor• The combined use of primidone and propranolol is more effective than either drug alone ($p < 0.05$).
*See full guideline for references.		

Conclusions

For limb tremor primidone and propranolol :

- Have similar efficacy when used as initial therapy
- Combined use possibly reduces tremor more than alone. There was no worsening of adverse events when used in combination
- Maintain anti-tremor efficacy in the majority of patients for at least one year

Evidence-based Recommendations

Level A

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

Evidence-based Recommendations

Level B

- Atenolol, gabapentin (monotherapy), sotalol, and topiramate should be considered for limb tremor (**Level B**).
- Alprazolam is recommended with caution due to its abuse potential (**Level B**).
- Propranolol should be considered for head tremor (**Level B**).

Evidence-based Recommendations

Level B

- Either primidone or propranolol may be used as initial therapy for limb tremor (**Level B**).
- Primidone and propranolol may be used in combination for limb tremor when monotherapy does not sufficiently reduce tremor (**Level B**).

Evidence-based Recommendations

Level C

- Nadolol and nimodipine may be considered when treating limb tremor in ET patients (**Level C**).
- Clonazepam should be used with caution due to its abuse potential and possible withdrawal symptoms (**Level C**).

Evidence-based Recommendations

Level C

- Clozapine is recommended only for refractory cases of limb tremor in ET due to the risk of agranulocytosis (**Level C**).
- The dosages of propranolol and primidone may need to be increased by 12 months of therapy when treating limb tremor in ET (**Level C**).

Evidence-based Recommendations Against therapies

Level A

Against pharmacologic agents

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

Evidence-based Recommendations Against therapies

Level B

Against Pharmacologic Treatments

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

Evidence-based Recommendations Against therapies

Level C

Against Pharmacologic Treatments

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

Evidence-based Recommendations

Level U

Insufficient evidence for Pharmacologic Treatments

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**).

Botulinum toxin treatment for ET

- Botulinum toxin effectiveness in patients with ET

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Botulinum Toxin A (hand tremor)	C	6	Moderate	20% CRS and 27% kinetic tremor
Botulinum Toxin A (head tremor)	C	3	Mild-moderate	Moderate - marked improvement by CRS; 67% accelerometry,

Mean improvement by CRS***or accelerometry compared to baseline

*See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients. ***CRS=Clinical Rating Scale

Analysis of Evidence

Intervention	Level of Evidence	# of Studies *	Adverse Events Severity**	Magnitude of Effect
Botulinum Toxin A (voice tremor)	C	3	Mild-moderate	22% unilateral injection, 30% with bilateral injection, 67% improvement in self-report

Mean improvement by CRS***or accelerometry compared to baseline

*See full guideline for references. **Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients. ***CRS=Clinical Rating Scale

BTX A

- Effect on limb tremor is modest,
- Associated with dose-dependent hand weakness
- May reduce head tremor and voice tremor, but data is limited

Evidence-based Recommendations

Level C

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).

Surgical treatments for ET

- Efficacy of thalamotomy in treating contra-lateral limb tremor
- Efficacy of deep brain stimulation (DBS) of the thalamus in treating refractory tremor
- Thalamotomy or DBS of the thalamus for patients with medically refractory ET
- Indications for bilateral versus unilateral surgical procedures
- Efficacy of Gamma Knife thalamotomy

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Chronic Thalamic DBS (Hand)	C	24	Mild - severe	60% to 90% CRS
Chronic Thalamic DBS (Head)	U	3	Mild - severe	n/a
Chronic Thalamic DBS (Voice)	U	1	Mild - severe	n/a

*See full guideline for references .**Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients.

***CRS=Clinical Rating Scale

Analysis of Evidence

Intervention	Level of Evidence	# of Studies*	Adverse Events Severity**	Magnitude of Effect
Unilateral vs. Bilateral DBS (Hand)	U	1	More frequent with bilateral surgery	n/a
Thalamotomy	C	8	Mild - severe	55% to 90% CRS
Gamma Knife Surgery	U	2	Mild - severe	70%-85% CRS

*See full guideline for references .**Adverse Events Severity: Mild: Somewhat bothersome; Moderate: Very bothersome; Severe: Potentially harmful to patients.

***CRS=Clinical Rating Scale

Conclusions

- Unilateral thalamotomy treats contra-lateral limb tremor.
- Bilateral thalamotomy is associated with more frequent and severe side effects.
- DBS of the VIM nucleus of the thalamus reduces contra-lateral limb tremor in medically refractory ET.
- There are conflicting data regarding the use of DBS to treat head or voice tremor.

Conclusions

- Both DBS and thalamotomy suppress tremor.
- There is insufficient data regarding the preferential use of unilateral or bilateral procedures for DBS.
- Several studies have found favorable results with gamma knife thalamotomy, but delayed complications have been reported, and clinical effects may take weeks to month to occur.

Evidence-based Recommendations

Level B

- DBS should be considered because it 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 frequent stimulator monitoring and adjustments.

Evidence-based Recommendations

Level C

- Unilateral thalamotomy may be used to treat limb tremor in ET that is refractory to medical management (**Level C**), while bilateral thalamotomy is not recommended due to adverse side effects (**Level C**).
- DBS of the VIM nucleus of the thalamus may be used to treat medically refractory limb tremor in ET (**Level C**).

Evidence-based Recommendations

Level U

- There is insufficient evidence to make recommendations regarding the use of gamma knife thalamotomy to treat ET (**Level U**).
- There is insufficient evidence to make recommendations regarding the use of DBS to treat head or voice tremor (**Level U**).

Evidence-based Recommendations

Level U

- There is insufficient evidence to make recommendations regarding the choice of unilateral or bilateral procedures for DBS (**Level U**). Bilateral thalamotomy is not recommended to treat limb tremor in ET due to adverse side effects.



Future Research

Research on treatment of ET is limited. Future research considerations include the following:

- Standardize outcome measures to assess tremor and to correlate accelerometry with clinical rating scales. To determine the magnitude of effect of pharmacological or surgical treatments.
- Knowledge of clinical and pathological heterogeneity of ET and how these relate to profiles of pharmacological responsiveness to help guide clinicians in selecting appropriate medications for their patients.



Future Research

- Determine the cost versus benefit profile for treatments.
- Assess the safety and efficacy of treatment of head and voice tremor.
- Further randomized, prospective, double-blind, placebo-controlled trials are needed to better determine the efficacy and side effect profiles of pharmacological and surgical therapies for ET.



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