Complete Summary

GUIDELINE TITLE

Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, Ondo WG, Gronseth GS, Weiner WJ. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005 Jun 28;64(12):2008-20. [100 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- On February 15, 2006, Bayer and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the prescribing information for nimodipine (Nimotop), including a boxed warning to notify prescribers about medication administration errors. When administered intravenously or parenterally, it can cause serious adverse events, including death. Nimodipine must not be administered intravenously or by any parenteral route. See the FDA Web site for more information.
- On January 13, 2006, Novartis and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of revisions to the BOXED WARNING, WARNINGS, CONTRAINDICATIONS, PRECAUTIONS (Information for Patients and Pharmacokinetic-Related Interactions subsections), and ADVERSE REACTIONS (Postmarketing Clinical Experience subsection) sections of the prescribing information for Clozaril (clozapine) tablets. Recommendations from the FDA's Psychopharmacological Drugs Advisory Committee regarding the white blood cell monitoring schedule, required for all clozapine users, has resulted in modification in the monitoring schedule. Additional labeling changes address safety issues related to dementia-related psychosis, parlytic ileus, hypercholesterolemia and pharmacokinetic interaction with citalopram. See the FDA Web site for more information.

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SCOPE

DISEASE/CONDITION(S)

Essential tremor (ET)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurological Surgery
Neurology

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians

GUIDELINE OBJECTIVE(S)

- To answer the following questions with regard to the pharmacologic treatment for essential tremor (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?
- To answer the following questions with regard to the 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 deep brain stimulation 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?

TARGET POPULATION

Patients with essential tremor (ET)

INTERVENTIONS AND PRACTICES CONSIDERED

Pharmacologic Treatment

1. Propranolol (Inderal)
2. Propranolol LA (Inderal LA)
3. Primidone (Mysoline)
4. Alprazolam (Xanax)
5. Atenolol (Tenormin)
6. Gabapentin (Neurontin) as monotherapy
7. Sotalol (Sotacor)
8. Topiramate (Topamax)
9. Clonazepam (Klonopin)
10. Clozapine (Clozaril)
11. Nadolol (Corgard)
12. Nimodipine (Nimotop)
13. Botulinum toxin A
14. Considered, but not recommended:
    - Trazodone (Desyrel)
    - Acetazolamide (Diamox)
    - Isoniazid (Laniazid, Nydrazid)
    - Pindolol (Visken)
    - Methazolamide (Neptazane)
    - Mirtazapine (Remeron)
    - Nifedipine (Adalat, Procardia)
    - Verapamil (Calan)
    - Amantadine (Symmetrel)
    - Clonidine (Catapres)
    - Gabapentin as adjunct therapy
    - Glutethimide (Doriden)
    - L-tryptophan/pyridoxine
    - Metoprolol (Lopressor, Toprol)
    - Nicardipine (Cardene)

- Olanzapine (Zyprexa)
- Phenobarbital (Luminal)
- Quetiapine (Seroquel)
- Theophylline (Theo-dur)

Nonpharmacologic (Surgical) Therapy

1. Chronic thalamic deep brain stimulation (DBS) (recommended for limb tremor, but not recommended for head or voice tremor)
2. Thalamotomy
    - Unilateral
    - Bilateral (considered, but not recommended)
3. Gamma knife thalamotomy (considered, but not recommended)

MAJOR OUTCOMES CONSIDERED

- Tremor suppression (magnitude of effect, duration of effect)
- Adverse events severity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Panel Selection and Literature Review Process

Neurologists with expertise in essential tremor (ET) were invited by the Quality Standards Subcommittee (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.

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, beta-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, ventral intermediate (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.

NUMBER OF SOURCE DOCUMENTS

211 articles were accepted for further review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

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 randomized controlled trial 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).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Each of the articles accepted for review was classified by two panel members using a four-tiered classification scheme that was developed and approved by the Quality Standards Subcommittee (QSS) (see "Rating Scheme for the Strength of the Evidence" field above). Analysis of evidence is summarized in Tables 1 and 2 of the original guideline document.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When formulating the recommendations the guideline developers considered the magnitude of the effect (benefit or harm of therapy, accuracy of tests, yield of studies) and the relative value of various outcomes. Under most circumstances, there is a direct link between the level of evidence used to formulate conclusions and the strength of the recommendation. Thus, an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation; a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation; a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation. In those circumstances where the evidence indicates that the intervention is not effective or useful, wording was modified. For example, if multiple adequately powered class I studies demonstrated that an intervention is not effective, the recommendation read, "should not be done."

There are important exceptions to the rule of having a direct linkage between the level of evidence and the strength of recommendations. Some situations where it may be necessary to break this linkage are listed below:

- A statistically significant but marginally important benefit of the intervention is observed
- The intervention is exorbitantly costly
- Superior and established alternative interventions are available
- There are competing outcomes (both beneficial and harmful) that cannot be reconciled

Under such circumstances the guideline developers may have downgraded the level of the recommendation.

Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

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.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Guidelines were approved by the Quality Standards Subcommittee (QSS) on July 24, 2004, by the Practice Committee on January 29, 2005, and by the American Academy of Neurology (AAN) Board of Directors on February 26, 2005.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, and U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

Pharmacologic Treatment of Essential Tremor (ET)

1. Propranolol, propranolol LA, or primidone should be offered to patients who desire treatment for limb tremor in essential tremor (ET), depending on concurrent medical conditions and potential side effects (**Level A**).
2. Either primidone or propranolol may be used as initial therapy to treat limb tremor in ET (**Level B**).
3. 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**).

4. 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**).
5. Trazodone is not recommended for treatment of limb tremor in ET (**Level A**).
6. Acetazolamide, isoniazid, and pindolol are not recommended for treatment of limb tremor in ET (**Level B**).
7. Methazolamide, mirtazapine, nifedipine, and verapamil are not recommended for treatment of limb tremor in ET (**Level C**).
8. 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**).
9. Primidone and propranolol may be used in combination to treat limb tremor when monotherapy does not sufficiently reduce tremor (**Level B**).
10. The dosages of propranolol and primidone may need to be increased by 12 months of therapy when treating limb tremor in ET (**Level C**).
11. Botulinum toxin (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 Treatment of ET

1. 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**).
2. Deep brain stimulation (DBS) of the ventral intermediate (VIM) thalamic nucleus may be used to treat medically refractory limb tremor in ET (**Level C**).
3. There is insufficient evidence to make recommendations regarding the use of thalamic DBS for head or voice tremor (**Level U**).
4. 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.
5. 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.
6. There is insufficient evidence to make recommendations regarding the use of gamma knife thalamotomy in the treatment of ET (**Level U**).

Definitions:

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

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 randomized controlled trial 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).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of essential tremor

POTENTIAL HARMS

Adverse events of medications and procedures. Refer to Tables 1 and 2 of the original guideline document for adverse effects of specific medications and procedures.

CONTRAINDICATIONS

CONTRAINDICATIONS

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. 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, or consult with a cardiologist.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology (AAN). 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, Ondo WG, Gronseth GS, Weiner WJ. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005 Jun 28;64(12):2008-20. [100 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Jun

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the American Academy of Neurology Web site.
- Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p. Electronic copies available in Portable Document Format (PDF) from the AAN Web site.
- Practice parameter: therapies for essential tremor. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.
- Practice parameter: therapies for essential tremor. St. Paul (MN): American Academy of Neurology. 2005. 21 p. Available for personal digital assistant (PDA) download from the AAN Web site.
- Practice parameter: therapies for essential tremor. Slide presentation. St. Paul (MN): American Academy of Neurology. Available as a PowerPoint file from the AAN Web site.

- Therapies for essential tremor. CME quiz. Available online to subscribers of *Neurology* at the Neurology Web site.

PATIENT RESOURCES

The following is available:

- Treatment for essential tremor. AAN guideline summary for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on July 26, 2005. The information was verified by the guideline developer on August 19, 2005. This summary was updated by ECRI on January 18, 2006, following the U.S. Food and Drug Administration advisory on Clozaril (clozapine). This summary was updated by ECRI on February 16, 2006, following the FDA advisory on Nimotop (nimodipine).

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