Evidence-based guideline update: Treatment of essential tremor
Report of the Quality Standards Subcommittee of the American Academy of Neurology

ABSTRACT

Background: This evidence-based guideline is an update of the 2005 American Academy of Neurology practice parameter on the treatment of essential tremor (ET).

Methods: A literature review using MEDLINE, EMBASE, Science Citation Index, and CINAHL was performed to identify clinical trials in patients with ET published between 2004 and April 2010.

Results and Recommendations: Conclusions and recommendations for the use of propranolol, primidone (Level A, established as effective); alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective); nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy (Level C, possibly effective); and gamma knife thalamotomy (Level U, insufficient evidence) are unchanged from the previous guideline. Changes to conclusions and recommendations from the previous guideline include the following: 1) levetiracetam and 3,4-diaminopyridine probably do not reduce limb tremor in ET and should not be considered (Level B); 2) flunarizine possibly has no effect in treating limb tremor in ET and may not be considered (Level C); and 3) there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U). Neurology® 2011;77:1752–1755

GLOSSARY

AAN = American Academy of Neurology; DBS = deep brain stimulation; ET = essential tremor; FTM = Fahn-Tolosa-Marin; TRS = Tremor Rating Scale.

Essential tremor (ET) is the most common tremor disorder and often affects activities of daily living, including writing and eating. The head and voice are commonly affected. Diagnostic criteria for ET may be found in the Consensus Statement of the Movement Disorder Society on Tremor.

Propranolol and primidone are the medications used most frequently and successfully to treat ET, and propranolol is the only medication approved by the US Food and Drug Administration to treat ET. Unfortunately, 30% to 50% of patients will not respond to either primidone or propranolol. This evidence-based guideline is an update of the American Academy of Neurology (AAN) 2005 practice parameter regarding treatment of ET and includes relevant research published since the 2005 publication.

DESCRIPTION OF THE ANALYTIC PROCESS

The AAN invited neurologists with expertise in ET to perform the review. Computer-assisted literature searches were conducted for relevant English-language articles pertinent to the treatment of ET. The MEDLINE, EMBASE, Science Citation Index, and CINAHL databases were searched from the years 2004 to 2010. Appendix e-1 on the Neurology® Web site at www.neurology.org lists the key words and phrases used in the search.

The search identified 589 articles pertaining to the treatment of ET, the titles and abstracts of which were each reviewed by at least 2 committee members. Articles were accepted for further review if they consisted of controlled trials, observational studies, cohort studies, open-label studies, or case series. Of the...
Pharmacologic agents with evidence supporting new conclusions or recommendations. Levetiracetam. One Class I study and 2 Class II studies investigated the efficacy of levetiracetam in ET. The randomized, crossover Class I study evaluated the acute effects of a single dose of levetiracetam on limb tremor and found some improvement in line drawing at 70 and 130 minutes ($p < 0.007$), whereas other tests did not show improvement (handwriting at 70 and 130 minutes and spirals at 70 minutes). Because the clinical relevance of the short-term outcome in this Class I study is unclear, the study was not considered further. Two Class II randomized, crossover studies showed no benefit of levetiracetam for ET.7,10

Conclusion. Levetiracetam probably does not reduce limb tremor in ET (2 Class II studies).

3,4-Diaminopyridine. One adequately powered Class I study failed to find any improvement in ET with 3,4-diaminopyridine.11

Conclusion. 3,4-Diaminopyridine probably does not reduce limb tremor in ET (1 Class I study).

Flunarizine. Flunarizine is a selective calcium channel blocker. Two Class III studies using blinded video analysis found flunarizine to be ineffective in treating ET.12,13

Conclusion. Flunarizine possibly has no effect in reducing limb tremor in ET (2 Class III studies).

Pregabalin. The effect of pregabalin on tremor was evaluated in 2 Class II studies. One study was a randomized, parallel-group, double-blind, placebo-controlled trial of 22 patients with ET.14 Pregabalin was initiated at 50 mg/day and escalated by 75 mg/day every 4 days to a maximum dose of 600 mg/day. Significant reduction in tremor amplitude in the pregabalin group at a mean dose of 286 mg/day and improvement in action tremor limb scores on the Fahn-Tolosa-Marin (FTM) Tremor Rating Scale (TRS) were observed. A second Class II randomized, crossover study of pregabalin in 20 patients with ET found no improvement in any of the TRS measures and a significant worsening of Quality of Life in Essential Tremor Questionnaire scores.15 Patients were treated with pregabalin (150–600 mg/day) or placebo, titrated over 6 weeks. Reported adverse events in these studies included drowsiness and dizziness.

Conclusion. The evidence is insufficient to support or refute the efficacy of pregabalin for ET (conflicting Class II studies).

Zonisamide. The effect of zonisamide, an antiepileptic medication, in ET was investigated in 2 Class III and several open-label studies.16–18 One Class III double-blind, placebo-controlled, randomized trial evaluated the efficacy and tolerability of zonisamide in treating ET in 20 patients at a mean dose of 160 ± 50 mg/day.17 No significant improvements in the FTM total score or its subsections were observed at the study end.
point, although tremor amplitude as assessed by acceler-
ometry significantly improved in the zonisamide group
at endpoint relative to baseline. Another evaluator-
blinded Class III study found significant improvements
in FTM rating scores in patients treated with zoni-
samide in both the blinded treatment phase and the
open-label extension phase, with mean doses of zoni-
samide of 252 mg/day and 225 mg/day, respectively.16

Conclusion. The evidence is insufficient to support
or refute the efficacy of zonisamide for ET (conflict-
ing Class III studies).

Clozapine. Clozapine, an antipsychotic medication
that received a Level C recommendation in the 2005
practice parameter, has been downgraded to a Level U
recommendation because of a trial that evaluated the
acute effects of clozapine in a controlled setting, fol-
lowed by a chronic open-label phase of the study in
“responders”19 (Level U for chronic use).

Conclusion. The evidence is insufficient to support
or refute the efficacy of clozapine for chronic use in
the treatment of ET.

NEW RECOMMENDATIONS Levetiracetam and
3,4-diaminopyridine should not be considered for
treatment of limb tremor in ET (Level B).

Clinicians may choose not to consider flunarizine
for treatment of limb tremor in ET (Level C).

The evidence is insufficient to make recommend-
ations regarding the use of pregabalin, zonisamide,
or clozapine (Level U).

CLINICAL CONTEXT Flunarizine use may result in
development of movement disorders, including
akathisia, dyskinesia, dystonia, and parkinsonism.

As an atypical neuroleptic agent, olanzapine can
induce parkinsonism. A review of 11 published stud-
ies of olanzapine use in patients with PD found re-
ports of worsening parkinsonism in 64 of 145
patients (44%).20 However, this side effect was not
observed in the study of patients with ET.

ET is a common movement disorder, and Class I
evidence supports the successful use of primi-
done and propranolol in ET treatment. However,
not all patients improve on or tolerate these medi-
cations. A survey of 223 patients in a clinical data-
base revealed that 70.9% had taken primidone or
propranolol, and 56.3% had discontinued one or
both medications.21 Thus, these first-line medica-
tions for ET clearly fail to meet the needs of many
patients.

RECOMMENDATIONS FOR FUTURE RESEARCH
Controlled clinical trials of additional medications
are needed using standardized outcome measures of
tremor, including disability scales and cost-benefit
analyses. The pursuit of better treatments for ET is ham-
pered by our limited understanding of the patho-
physiology of ET. Despite its high prevalence, few
postmortem studies had historically been conducted.
Recent postmortem evidence, however, indicates the
presence of a heterogeneous set of degenerative
changes in the brains of people with ET, indicating
that ET is likely to be a syndrome or family of dis-
eases rather than a single disease, which adds a layer
of complexity to matters. Furthermore, the sequence
of molecular events that underlie these degenerative
changes has yet to be elucidated, and until such a
time, it will be difficult to design specific targets for
pharmacotherapeutic intervention.

AUTHOR CONTRIBUTIONS

Dr. Zesiewicz: drafting/revising the manuscript, study concept or design,
analysis or interpretation of data, acquisition of data, study supervision.
Dr. Elble: drafting/revising the manuscript, study concept or design, anal-
ysis or interpretation of data, acquisition of data, Dr. Louis: drafting/
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K.L. Sullivan: drafting/revising the manuscript. Dr. Weiner: drafting/
revising the manuscript, study concept or design, analysis or interpre-
tation of data, acquisition of data, study supervision.

DISCLOSURE

Dr. Zesiewicz serves on the speakers’ bureau for and has received funding
for travel and speaker honoraria from Teva Pharmaceutical Industries
Ltd.; serves on the editorial board of Tremor and Other Hyperkinetic Move-
dment Disorders; serves as a consultant for Boehringer Ingelheim,
Teva Pharmaceutical Industries Ltd., Allergan, Inc., UCB, and Novartis;
and is listed as an inventor on a provisional patent on the use of nicotinic
modulators in treating ataxia and imbalance held by the University of
South Florida; and receives has received research support from Pfizer Inc.,
the National Ataxia Foundation, the Friedreich’s Ataxia Research Associa-
tion, and the Bobby Allison Ataxia Research Center. Dr. Elble serves on
the scientific advisory board for the International Essential Tremor Foun-
dation; has received funding for travel from the Movement Disorders
Society; receives research support from GlaxoSmithKline, Teva Pharma-
aceutical Industries Ltd., Pfizer Inc., Phytopharm, Janssen (Ortho-
McNeil), the NIH/NINDS, and the Spastic Paralysis Research
Foundation of Kiwanis International; and has acted as an expert witness in
a medico-legal proceeding. Dr. Louis has received honoraria from the
American Academy of Neurology; receives research support from the
NIH/NINDS and the Parkinson’s Disease Foundation; and has served as
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can Academy of Neurology. Dr. Ondo has received speaker honoraria
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and Lundbeck Inc.; serves on the editorial board of Tremor and Other
Hyperkinetic Movements; receives publishing royalties for Restless Leg Syn-
drome: Diagnosis and Treatment (Informa, 2008) and Handbook of Move-
dment Disorders (Wiley-Blackwell, 1998); and has received research support
from Takeda Pharmaceutical Company Limited, ACADIA Pharmaceuticals,
Ipsen, IMPAX Laboratories, Inc., XenonPort, Inc., Bayer Schering
Pharma, and Allergan, Inc. Dr. Dewey serves on the speakers’ bureaus for
and has received funding for travel and speaker honoraria from Teva Phar-
maceutical Industries Ltd., GlaxoSmithKline, Ipsen, Boehringer Ingel-
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CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbs commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, Neurology peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

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REFERENCES


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