SPECIAL ARTICLE

Evidence-based guideline update: Treatment of essential tremor

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

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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.

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Essential tremor (ET) is the most common tremor disorder and often affects activities of daily living, including writing and eating.[1] 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.[2]

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.[3] This evidence-based guideline is an update of the American Academy of Neurology (AAN) 2005 practice parameter regarding treatment of ET[4] 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

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589 articles, 252 were reviewed in their entirety. Panel members who were authors of reviewed studies did not grade their own research.

ANALYSIS OF EVIDENCE **Pharmacologic agents without evidence to change the conclusions or recommendations.** There were no additional trials published since the previous guideline and rated better than Class IV that examined the efficacy and safety of propranolol, primidone, alprazolam, atenolol, gabapentin (monotherapy), sotalol, propranolol for head tremor, clonazepam, nadolol, nimodipine, botulinum toxin, clozapine, acetazolamide, isoniazid, pindolol, trazodone, methazolamide, mirtazapine, nifedipine, verapamil, sodium oxybate (in ethanol-sensitive ET), oxcarbazepine, tiagabine, amantadine, clonidine, gabapentin (adjunct therapy), glutethimide, l-tryptophan/pyridoxine, metoprolol, nicardipine, phenobarbital, quetiapine, and theophylline.[4]

Several new Class II studies addressed the efficacy of topiramate for ET.[5,6] The results of these studies confirmed those of previous studies showing efficacy of topiramate for ET and do not lead to a change in the previous guideline's recommendation. Table e-1 summarizes the previous conclusions and recommendations regarding pharmacologic interventions.

Olanzapine. Olanzapine, an atypical antipsychotic, was compared with propranolol in one Class III study of limb tremor.[7] Thirty-eight patients were randomized to receive olanzapine (20 mg/day) or propranolol (120 mg/day) in a crossover study and were evaluated at baseline and after 1 month. Propranolol and olanzapine significantly reduced scores on all evaluation measures, although a placebo effect cannot be ruled out. The evidence is insufficient to support or refute the efficacy of olanzapine for ET (single Class III study).

Surgical interventions without evidence to change the conclusions or recommendations. There were no additional trials rated better than Class IV that examined the efficacy and safety of thalamotomy for contralateral limb tremor, gamma knife thalamotomy, or deep brain stimulation (DBS) of the thalamus for the treatment of ET. Moreover, no additional trials rated greater than Class IV were available that assessed the relative efficacy of thalamotomy vs thalamic DBS, bilateral vs unilateral surgical procedures, or direct subthalamic vs zona incerta/prelemniscal stimulation.[4] Table e-2 summarizes the previous conclusions and recommendations pertaining to surgical interventions.

Clinical context. No high-quality, long-term studies exist regarding the efficacy and safety of these interventions for ET.

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).[8] 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.[9,10]

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 accelerometry 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 zonisamide in both the blinded treatment phase and the open-label extension phase, with mean doses of zonisamide 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 (conflicting 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, followed 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 recommendations 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 studies of olanzapine use in patients with PD found reports 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 primidone and propranolol in ET treatment. However, not all patients improve on or tolerate these medications. A survey of 223 patients in a clinical database revealed that 70.9% had taken primidone or propranolol, and 56.3% had discontinued one or both medications.[21] Thus, these first-line medications 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 hampered by our limited understanding of the pathophysiology 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 diseases 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, analysis or interpretation of data, acquisition of data. Dr. Louis: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Gronseth: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Ondo: drafting/revising the manuscript, acquisition of data. Dr. Dewey: drafting/revising the manuscript. Dr. Okun: drafting/revising the manuscript, analysis or interpretation of data, study supervision, critical revision. K.L. Sullivan: drafting/revising the manuscript. Dr. Weiner: drafting/revising the manuscript, study concept or design, analysis or interpretation 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 Movement Disorders*; serves/has served as a consultant for Boehringer Ingelheim, Teva Pharmaceutical Industries Ltd., Allergan, Inc., UCB, and Novartis; 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 Association, and the Bobby Allison Ataxia Research Center. Dr. Elble serves on the scientific advisory board for the International Essential Tremor Foundation; has received funding for travel from the Movement Disorders Society; receives research support from GlaxoSmithKline, Teva Pharmaceutical 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 a legal consultant on epidemiologic issues. Dr. Gronseth serves on the editorial advisory board of *Neurology Now*, serves on the speakers' bureau for Boehringer Ingelheim, and receives research support from the American Academy of Neurology. Dr. Ondo has received speaker honoraria from GlaxoSmithKline, Boehringer Ingelheim, Allergan, Inc., Teva Pharmaceutical Industries Ltd., Novartis, Ipsen, Merz Pharmaceuticals, LLC, and Lundbeck Inc.; serves on the editorial board of *Tremor and Other Hyperkinetic Movements*; receives publishing royalties for *Restless Legs Syndrome: Diagnosis and Treatment* (Informa, 2008) and *Handbook of Movement Disorders* (Wiley-Blackwell, 1998); and has received research support from Takeda Pharmaceutical Company Limited, ACADIA Pharmaceuticals, Ipsen, IMPAX Laboratories, Inc., XenoPort, 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 Pharmaceutical Industries Ltd., GlaxoSmithKline, Ipsen, Boehringer Ingelheim, and Allergan Inc.; serves as a consultant for Teva Pharmaceutical

Industries Ltd.; receives research support from the NIH; and has served as an expert witness in a medico-legal case. Dr. Okun serves on scientific advisory boards for the Dystonia Medical Research Foundation and the National Parkinson Foundation and the Medical Advisory Board for the Tourette Syndrome Association; has received funding for travel and speaker honoraria from Medtronic, Inc. prior to 2010; has served/serves on the editorial boards of *Neurology*® and *Parkinsonism and Related Disorders*; is a founder of the COMPRESS software used for deep brain stimulation (DBS) screening and has filed patents regarding double lead DBS, DBS targeting, and COMPRESS; receives royalties from the publication of *Ultimate Neurology Review* (DEMOS, 2007), *Parkinson's Disease* (Manson, 2009), and *Deep Brain Stimulation for Neurological and Psychiatric Diseases* (Humana Press, 2009); serves as Medical Director of the National Parkinson Foundation and as a member of the Ask the Expert Forum; and has received research support from Medtronic, Inc. (devices and training fellowship grants), the NIH, the University of Florida Foundation, the Parkinson Alliance, the Michael J. Fox Foundation, and the National Parkinson Foundation. K.L. Sullivan reports no disclosures. Dr. Weiner has served on scientific advisory boards for Santhera Pharmaceuticals and Rexahn Pharmaceuticals, Inc.; serves on the editorial boards of *Parkinsonism and Related Disorders* and *Neurological Reviews* and as Editor of *Treatment Options in Neurology*; receives royalties from the publication of *Neurology for the Non-Neurologist* (6th edition, Wolters Kluwer/Lippincott, 2010), *Parkinson's Disease: A Complete Guide for Patients and Family* (2nd edition, Hopkins University Press, 2007), and *Handbook of Clinical Neurology Hyperkinetic Disorders* (Elsevier, 2011); has received research support from Novartis, Santhera Pharmaceuticals, and Boehringer Ingelheim; and has provided expert testimony and served as a subject matter expert in legal proceedings.

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. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

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 forbids 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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