Tremor Guideline Reconsiders Some Therapies

BY JENNIE SMITH

FROM NEUROLOGY

A new evidence-based guideline issued by the American Academy of Neurology for the treatment of essential tremor reinforces the use of propranolol and primidone as the go-to agents for the disease.

However, these first-line agents – used as monotherapy or combination therapy since the 1980s – do not work in between 30% and 50% of people with essential tremor (ET). Moreover, a 2010 study of 223 ET patients in a clinical database revealed that more than half of patients taking primidone and/or propranolol had discontinued them, suggesting that the need for alternatives is great (Parkinsonism Relat. Disord. 2010;16:604-7). Primidone and propranolol are known to cause side effects at higher doses.

Essential tremor is a common, progressive neurological disease, formerly called "benign essential tremor," that causes a rhythmic trembling of the hands, head, voice, legs, or trunk, and is sometimes mistaken for Parkinson's disease.

In its new ET guideline, published online Oct. 19 as an update of its 2005 guideline for ET, the AAN continues to recommend topiramate, alprazolam, atenolol, gabapentin, and sotalol as second-line treatments, based on clinical evidence that they are probably effective. The AAN's new recommendations are based on reviews of 589 articles (252 of these complete reviews) of randomized controlled trials, observational studies, cohort studies, and case series published between 2004 and 2010 (Neurology 2011 Oct. 19 [Epub ahead of print]).

The AAN's team of reviewers, led by Dr. Theresa A. Zesiewicz of the University of South Florida in Tampa, found that they could not recommend levetiracetam and 3,4-diaminopyridine as second-line agents, based on quality (level B) clinical evidence that they do not reduce limb tremor. The evidence on flunarizine suggests that it is probably ineffective in reducing limb tremor. And the reviewers could not recommend pregabalin, zonisamide, and clozapine, based on insufficient evidence to support or refute their use in ET.

The reviewers could not recommend levetiracetam and 3,4-diaminopyridine as second-line agents, and evidence suggests that flunarazine is not effective in reducing limb tremor.

"There were some agents we had some hopes for that didn't pan out, and levetiracetam was one of them," Dr. Zesiewicz said in an interview, adding that patients not responding to primidone or propranolol, or in whom these are contraindicated, might benefit from any of the currently recommended second-line agents with level B evidence supporting them. Of these, she said, topiramate is supported by the largest cohort studies, but "any of the level B, or level C agents" can be tried. Surgical interventions in ET patients, though seen to have greater treatment effect than medications, are seldom tried before a second-line agent doesn't work and a tremor becomes debilitating. "The reason we don't go to [surgery] right away is because when the side effects do occur – which is relatively rare – they can be serious," Dr. Zesiewicz said.

The guideline's advice on surgical interventions for ET remain unchanged from 2005, with deep brain stimulation (DBS) still recommended. DBS, by which a device is implanted in the brain to transmit electrical impulses, "has really become the surgery of choice," Dr. Zesiewicz said.

There is still too little evidence for the AAN to recommend gamma knife thalamotomy, which uses targeted radiotherapy, and concern remains about rare but serious side effects with the procedure. Nonetheless, "the story about gamma knife has yet to be completely written," Dr. Zesiewicz said.

Another surgical intervention currently being explored, which uses MR-

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EVOKED POTENTIALS

Group Creativity Requires Knowledge, Leadership

Our creativity as a species stems in part from our ability to use knowledge passed from older generations and to receive guidance from leaders in how to use it in new ways. The shared mission of neurologists within their own groups, departments, and institutions, and within the specialty, is no exception. But our ability to work together and accept the direction of leaders is relatively new in *Homo sapiens*' roughly 200,000-year-old existence. In that time, it took 195,000 years to invent a wheel, 199,500 years to create a printing press, and 199,900 years to develop an automobile. Given that time frame, how can we account for this unprecedented leap in creativity if there was not enough time for natural selection's incremental physiological, structural, and genetic "improvements?"

RICHARD J. CASELLI, M.D.

Alfred Russell Wallace was a contemporary of Charles Darwin, and both proposed a theory of natural selection as the basis for the evolution of species. However, Wallace felt that the human mind was an exception to this theory. He posited a more spiritual explanation. Many regarded this scientific "softness" with derision, but his observation that natural selection was a poor explanation for man's unprecedented creative leap may have been more scientifically astute than Darwin's failure to question it. Many anthropologists currently agree with Wallace that incremental improvements alone fail to explain this behavioral leap. They instead explain it by human cultural evolution, which, in a nutshell, is the sharing of information within and across generations. The emergence of language probably made this sharing possible.

Homo sapiens' success in developing a cumulative culture is based on cooperation with both kin and nonkin, and exceptional reliance on cultural transmission within and across generations. This is rare or absent in other apes whose cooperative behaviors are much more closely kin focused. Kinship is an important organizing principle in primate social groups. In macaques, for example, as the genetic relatedness of members decreases within a group, the social instability of the group increases, resulting in more fighting and wounding (PLoS One 2011;6:e16365).

In contrast, primitive human hunter gatherer societies are 25% genetically unrelated, 50% distantly related, and only 25% closely related. This nonrelatedness fosters intergroup interactions that may lead to the spread of cooperative institutions. When people reside together they have frequent opportunities to observe innovations and imitate successful traits. The change in ancestral human residential structure, compared with our evolutionary ancestors, may have therefore led to greater exposure to more ideas of value and may explain why humans and no other animals developed the costly social learning mechanisms that have resulted in cultural evolution (Science 2011;331:1286-9). This increasingly complex social behavior is correlated with brain size, especially in the frontal neocortex.

The complexity and size of the 'creative unit' has become ever larger over time, using more knowledge and leadership, from the invention of the wheel to the development of the space shuttle.

The wheel and the space shuttle are both products of creativity, but among their many obvious differences is one we can call the "creative unit." The wheel's creative unit could have been a single person with all the tools needed to generate the first prototype, whereas the space shuttle clearly required many teams of people working together. Coordinating a team requires leadership. Effective leaders maintain high mutual cooperation among their group's members by ensuring that the penalty for noncooperation is fair and outweighed by any possible reward for noncooperation. Leaders must enforce social norms, rules, or laws. If mutual cooperation with a social norm is perceived by the membership to drop, then individual defection rates will rise and the previously defined social norm will break down (Trends Cogn. Sci. 2004;8:185-90). Saying something is so will work only as long as it usually is so, and it is the leader's role to maintain that consistency. One caveat is that leaders should also be perceived as tolerant. Few people have perfect track records of cooperation, and occasional minor missteps must be accommodated. In a study that looked at the reaction of leadership to such noncooperative behavior, it was shown that cooperative behavior in a social grouping is enhanced by perceived mercy of those in charge (Nature 2003;422:137-40). Consistency, fairness, and temperance in holding members accountable all matter in a leader's ability to foster cooperation.

This is the last installment of Dr. Caselli's 10-part series on creativity. Watch for next year's series on disorders of creativity.

Effective leaders create a culture of identity and mission, and foster belief in the group's competitive superiority so that the group believes it can win. The culture must distinguish the group's creative unit from others ("Myth and Meaning" [New York: Schocken Books, 1979, p. 20]). Within such a unit, teamwork will flourish and space shuttles will fly. Cooperation is enhanced by perceived similarity among a group's members. While this can apply to physical appearances, similarity is more defined in a business setting, research lab, or neurology department by a sense of shared mission. Just as the role of every member of NASA, from astronomer to janitor, is to put us into space, the mission of a health care organization, from the doctors to the secretaries, is to heal patients.

Jonathan Haidt in his book, "The Happiness Hypothesis" (New York: Basic Books, 2006), makes the compelling argument, drawing from the school of positive psychology, that virtue enhances happiness. Virtue, in this case, is defined broadly as excellence and involves morality. A leader who can cast the actions of the group as serving a noble cause can increase the group's level of happiness, and in this virtue-inspired happy state the group will be further motivated to work toward the virtuous goal. The shared sense of a virtuous mission creates a shared identity, and the competitive, proud sense that they will excel in achieving that mission.

We in the medical world have little problem believing that we have a virtuous mission. Let us continue to work as a team within our groups, institutions, specialty, and in the broader role we have in society to use our talents creatively and cooperatively so as to continue advancing our mission for neurologic health. ■

DR. CASELLI *is the medical editor of* CLINICAL NEUROLOGY NEWS *and is professor of neurology at the Mayo Clinic in Scottsdale, Ariz.*

LETTERS

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guided focused ultrasound, was not mentioned in the current guidance, but Dr. Zesiewicz called it "extremely interesting," and hopes that the procedure, pioneered by Dr. W. Jeffrey Elias of the University of Virginia, Charlottesville, will hold up in long-term safety studies and randomized controlled trials. "Gamma ray looked good too," she noted – until some rare but severe delayed adverse effects were seen.

Dr. Zesiewicz and her colleagues noted that more and larger randomized controlled trials, with standardized outcome measures, were needed for ET treatments.

"We lost a lot of ground in research because of the [former] name 'benign essential tremor,' " Dr. Zesiewicz said. "Once that 'benign' was dropped it became a more serious priority. Hopefully we'll be able to gain ground now that we know that this is a serious condition, it is a disease, and it's certainly not benign."

However, the pathology of ET, now thought to be a heterogeneous set of degenerative changes in the brain, has become much better understood in recent years, thanks to researchers' postmortem studies of the brains of ET patients at Columbia University in New York.

The Columbia brain bank's research is being led by Dr. Elan Louis, one of the new ET guideline's coauthors. Dr. Louis and colleagues have made "tremendous headway," Dr. Zesiewicz said, in elucidating the causes of ET.

Dr. Zesiewicz said she hopes new agents will be designed to target ET specifically. The currently recommended agents range from antiepileptics to medications used to treat schizophrenia – and only one, propranolol, is approved by the U.S. Food and Drug Administration to treat ET. (Even primidone is not FDA-approved, despite its widespread, long-term use.)

"What's important to understand is that ET may be a heterogeneous condition," Dr. Zesiewicz said. "When we pick that apart and truly understand the mechanisms by which ET occurs, we may be able to develop research and medications specific to the problem."

Dr. Zesiewicz disclosed having received speakers' fees other forms of support from Teva, Boehringer Ingelheim, Allergan, and Novartis, along with research support from Pfizer, and is an inventor on a provisional patent on the use of nicotinic modulators in treating ataxia and imbalance held by the University of South Florida. Several of Dr. Zesiewicz's coauthors on the ET guideline acknowledged support from these and other companies, including GlaxoSmithKline, Phytopharm, Janssen, Allergan, Novartis, Ipsen, Merz, Lundbeck, and Bayer. ■