Relias Media
From Relias

Vol. 41, Issue 3, November 2021
ReliasMedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Atogepant for Migraine Prevention

By Alina Masters-Israilov, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Atogepant, an oral small-molecule inhibitor of the calcitonin gene-related peptide pathway, administered once daily, effectively reduced migraine days in the preventive treatment trial of migraine over a period of 12 weeks.

SOURCE: Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med* 2021;385:695-706.

Calcitonin gene-related peptide (CGRP) has been shown to be involved in migraine pathophysiology and has been targeted in new migraine therapies. CGRP monoclonal antibodies (mAbs) affecting the receptor or ligand have been developed and in clinical use since 2018 for the prevention of migraine. Oral CGRP receptor antagonists (gepants) have been available more recently for abortive therapy of migraine attacks, although rimegepant also has been available for prevention since earlier in 2021. Ailani et al conducted a multicenter, double-blind, randomized, placebo-controlled trial with atogepant, an oral small-molecule CGRP receptor antagonist, for the prevention of episodic migraine. Atogepant reaches maximum plasma concentrations in one to two hours and has a half-life of approximately 11 hours.

The trial included a screening period (four weeks), baseline period (four weeks), double-blind treatment period (12 weeks), and a safety follow-up period (four weeks). Participants were between the ages of 18 and 80 years and had episodic migraine (four to 14 migraine days per month in the three months leading up to screening and in the 28-day baseline period). They were randomly assigned in a 1:1:1:1 fashion to receive either 10 mg, 30 mg, or 60 mg of atogepant or placebo daily during the treatment period. Exclusion criteria included patients with chronic migraine, history of inadequate response to more than four oral preventive medications, medication overuse headache, or plans to become pregnant. They were allowed to treat migraine attacks with abortive therapies but were not allowed to take any migraine preventive medication starting 30 days before their screening visit and throughout the duration of the trial. Participants recorded efficacy assessments in an electronic diary throughout the trial, documenting headache duration, clinical features of their headaches, and abortive therapies used. Additional data were collected through questionnaires and diaries. The primary endpoint was the change from baseline in the mean number

Financial Disclosure: Dr. Rubin (author) reports he is a consultant for Merck Sharpe & Dohme Corp. All of the relevant financial relationships listed for this individual have been mitigated. None of the remaining authors or planners for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Neurology [ALERT®]

Neurology Alert (ISSN 0741-4234) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Neurology Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Questions & Comments:
Please contact Jason Schneider at jschneider@relias.com.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

of migraine days per month across the 12-week treatment period. Adverse events were reported by the participants, and laboratory tests, vital stastistics, and electrocardiograms were checked as well.

A total of 910 participants were randomized, with 805 of them completing the trial. Baseline characteristics were comparable among the groups; participants had an average of 7.4 migraine days per month in the three months before randomization. The mean change from baseline in the mean number of migraine days per month across the 12-week treatment period was -3.7 with 10 mg atogepant, -3.9 with 30 mg atogepant, -4.2 with 60 mg atogepant, and -2.5 with placebo. The mean difference from placebo with all three doses of atogepant showed statistically significant results. A reduction of 50% or more in the three-month average of migraine days per month, an important secondary efficacy endpoint, occurred in 55.6% of the participants in the 10 mg atogepant group, 58.7% of those in the 30 mg atogepant group, 60.8% of those in the 60 mg atogepant group, and 29.0% of those in the placebo group ($P < 0.0001$ for all comparisons with placebo). Differences from placebo were observed within the first four weeks after initiation of treatment.

Adverse events were reported by 52.2% to 53.7% of the participants in the atogepant groups and by 56.8% of those in the placebo group. Constipation, nausea, and upper respiratory tract infection were the most commonly reported adverse events in the atogepant groups. The incidence of constipation was higher in the atogepant groups compared to placebo, although none of the cases of constipation were determined to be serious. A total of five participants in the atogepant groups and four participants in the placebo group had elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) levels.

■ COMMENTARY

Atogepant, at all three doses studied, was effective in reducing monthly migraine days compared to placebo over a 12-week trial period. The population studied had episodic migraine, so it is unclear if the same benefit would be seen in patients with chronic migraine. Long-term safety studies are needed, as well as inclusion of a more diverse group of participants. Atogepant may be an effective alternative for migraine prevention for patients who are anxious about self-injecting CGRP mAbs. It also may be considered instead of CGRP mAbs in women who may want to become pregnant in the very near future who would otherwise have to wait at least four to six months after stopping a CGRP mAb before conceiving, as opposed to several days after stopping atogepant. There also were fewer reported side effects with atogepant than with many historically used migraine prevention treatments, making it an attractive option for prevention. As with other new CGRP-based medications, drug cost and insurance drug coverage will be important factors in the practical availability of this medication to patients living with migraine. ■

ABSTRACT & COMMENTARY

Is the Suicidality Class Warning Warranted for Antiseizure Medications?

By Pegah Afra, MD

Associate Professor of Neurology, Weill Cornell Medical College; Associate Attending Neurologist; NewYork-Presbyterian Hospital; Adjunct Associate Professor, University of Utah

SYNOPSIS: This study reports data that refutes the U.S. Food and Drug Administration's class warning regarding suicidality risk in patients with epilepsy who are taking the newer antiepileptics, approved since 2008. The class warning should be reconsidered.

SOURCE: Klein P, Devinsky O, French J, et al. Suicidality risk of newer antiseizure medications: A meta-analysis. *JAMA Neurol* 2021;78:1118-1127.

The U.S. Food and Drug Administration (FDA) issued a class warning for antiseizure medications (ASMs) in 2008 regarding their increased suicidality risk (1.80-fold). This was based on meta-analysis of pooled data from 199 randomized, placebo-controlled clinical trials involving 11 ASMs: carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. There were a total of 43,892 patients in these 199 randomized placebo-controlled trials: 16,029 in the pooled placebo arm and 27,863 patients in the pooled drug arm (including 10,942 patients with epilepsy, 11,796 patients with psychiatric disorders, and 21,154 with other disorders [mainly pain]).[1]

Suicidality occurred in 4.3/1,000 patients in the pooled drug arm compared with 2.2/1,000 patients in the pooled placebo arm, with a risk difference of 2.1 per 1,000. In patients with epilepsy, suicidality rates were 3.4/1,000 with ASM treatment vs. 1/1,000 with placebo. Additionally, there were four completed suicides, all in the pooled drug arm (two patients with epilepsy and two patients with psychiatric disorders). The FDA advisory board concluded that all ASMs "pose an increased risk of suicidality (defined as suicidal ideation and behavior), and prescriptions should be accompanied by a patient medication guide describing this risk."[2] These recommendations have resulted in an FDA-mandated warning for suicidality in ASMs developed after 2008.[2] This class warning has influenced clinical practice as well as ASM investigational trial designs after 2008, including systematic and standardized assessment of suicidality done in clinical trials after 2011.

In this study by Klein et al, the risk of suicidality of newer ASMs (vs. placebo) was evaluated by reviewing all Phase II and III placebo-controlled adjunctive treatment trials of 10 ASMs approved after 2008. Primary articles were obtained and reviewed for frequency of suicidality, in total as well as in subcategories (frequency of suicidal ideation, attempts, and completed suicides). Studies that did not evaluate suicidality (everolimus and fenfluramine) or did not evaluate it prospectively (lacosamide, ezogabine, and clobazam) were excluded. Therefore, five ASMs were included: eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate.

These five ASMs were evaluated in 19 studies (16 pivotal [Phase II or III studies] and three nonpivotal studies and included three eslicarbazepine, four perampanel, six brivaracetam, four cannabidiol, and two cenobamate studies. Two of the four cannabidol studies were excluded because of the absence of suicidality evaluation, leaving 17 studies included. These 17 studies had 5,996 patients, and suicidality was evaluated in 4,000 patients treated with ASMs vs. 1,996 patients treated with placebo in the following subcategories:

1. Suicidal ideation: Present in 12/4,000 (0.30%) patients treated with ASM compared with 7/1,996 (0.35%) patients treated with placebo ($\chi^2 = 0.108$; $P = 0.74$);
2. Suicidal attempts: Present in 3/4,000 (0.075%) patients treated with ASM compared with no patients treated with placebo attempted suicide ($\chi^2 = 1.498$; $P = 0.22$);
3. Completed suicide: There were no completed suicides in either group.

There was no evidence of bias or heterogeneity between the placebo and treatment groups. The study found no evidence that the five ASMs (eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate) evaluated in this study increase suicidality in patients with epilepsy and, therefore, the FDA's suicidality class warning for these five ASMs does not seem to be warranted.

■ COMMENTARY

The FDA suicidality class warning issued in 2008 has affected both clinical management of epilepsy and ASM drug development. The FDA pooled analysis of 199 trials that was the basis of the suicidality class warning had its own methodological limitations, which are outside the scope of this commentary.[3] Overall, the 2008 issued class warning can influence clinical practice by affecting a patient's decision to start or adhere to ASMs (potentially increasing the risk of sudden unexpected death in epilepsy [SUDEP]). The risk of uncontrolled seizures may be higher than the risk of suicidality from the ASMs.

It also has altered clinical trials. Since 2013, all Phase I-III clinical trials have excluded patients with suicidal risk. The risk is higher in patients with uncontrolled epilepsy, resulting in a significant proportion of patients with uncontrolled epilepsy being excluded from these trials. It also makes it impossible to evaluate whether ASMs affect suicidality in these high-risk patients. As a result of mandating suicidality evaluations, many of the ASM clinical trials done after 2008 evaluate suicidality in a prospective manner. More specifically, studies conducted between 2008 and 2011 did not assess suicidality in systematic and standardized ways, while studies conducted in 2011 and thereafter did.

Pooling this prospective suicidality data for the five ASMs listed earlier, the authors did not find any evidence to support the FDA's original class ruling for suicidality. This important finding may affect future development of ASM clinical trials, as well as clinical practice. ■

REFERENCES

1. U.S. Department of Health and Human Services. Statistical review and evaluation: Antiepileptic drugs and suicidality. https://www.fda.gov/files/drugs/published/Statistical-Review-and-Evaluation--Antiepileptic-Drugs-and-Suicidality.pdf
2. Busko M. FDA advisory members agree antiepileptics pose suicidality risk, nix need for black-box warning. Medscape.

Published July 11, 2008. https://www.medscape.com/viewarticle/577432
3. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia* 2009;50:978-986.

ABSTRACT & COMMENTARY

Neurodegenerative Ataxia: Improvement in Motor and Cognitive Outcomes with Cerebello-Spinal Stimulation

By Mary L. Vo, MD, PharmD

Assistant Professor of Neurology, Weill Cornell Medical College

SYNOPSIS: Concurrent cerebellar and spinal stimulation with a transcranial direct current stimulation device resulted in improvement of both motor and cognitive functions in patients with several different forms of neurodegenerative ataxia.

SOURCE: Benussi A, Cantoni V, Manes M, et al. Motor and cognitive outcomes of cerebello-spinal stimulation in neurodegenerative ataxia. *Brain* 2021;144:2310-2321.

Cerebellar ataxic syndromes are a heterogenous group of disorders characterized by gait instability appendicular ataxia, tremor, oculomotor abnormalities, and cognitive impairment resulting in progressive disability. The pathophysiologic mechanism of both genetic and acquired cerebellar disorders involves cumulative injury from oxidative stress, mitochondrial dysfunction, impaired deoxyribonucleic acid (DNA) repair, and abnormalities in cytoskeletal proteins. The absence of effective treatments or robust symptomatic therapies represents a large unmet need in this population. A growing body of literature has shown the benefit of transcranial magnetic stimulation (TMS) therapy for ataxia. More recently, there has been increasing interest in transcranial direct current stimulation (tDCS) of the cerebellum and spinal cord, since these areas are implicated in cerebellar ataxia. Treatment with tDCS can improve motor symptoms in patients with cerebellar ataxia by promoting neuroplasticity and restoring cerebellar inhibition.

The authors of this study explored the short-term and long-term effects of tDCS treatments on motor and cognitive function in patients with cerebellar ataxia. Additionally, the study design aimed to compare the duration of measurable improvement and the effect of a single treatment compared to two treatments. The study is a randomized, double-blind, sham-controlled trial of 61 patients with cerebellar ataxia recruited from a single specialized neurodegenerative clinic in Brescia, Italy. The study included subjects with molecularly confirmed spinal cerebellar ataxia (SCA), multisystem atrophy-cerebellar type (MSA-C), Friedreich's ataxia, sporadic adult-onset ataxia, and cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS). All subjects had evidence of cerebellar or spinal cord atrophy on magnetic resonance imaging (MRI). Patients were randomized to receive sham stimulation vs. concurrent cerebellar and spinal tDCS over five sessions per week for two weeks. After a 12-week washout period, both groups were treated with tDCS administered in five sessions per week for two weeks in an open-label arm of the study. Primary outcome measures were change in motor score as measured by a scale for the assessment and rating of ataxia (SARA) and international cooperative ataxia rating scale (ICARS) as well as cognitive changes measured with cerebellar cognitive and affective syndrome scale (CCASS) scores. Secondary outcome measures were change in quality-of-life measures as well as cerebellar inhibition measured by transcranial magnetic stimulation. All assessments were conducted at weeks 0, 12, 14, 24, 36, and 52.

Statistical analysis used two-way analysis of covariance (ANCOVA) to assess changes in clinical scores and neurophysiologic measures over time and to measure differences between the two treatment groups. Post-hoc analysis with Hochberg's step-up procedure was employed to analyze group differences at each time point. Spearman rank-order correlations were used to evaluate associations between improvement in functional scores, neurophysiological parameter, and clinical characteristics. Twenty-eight subjects in group 1 received sham stimulation, whereas 33 subjects in group 2 were treated with tDCS. Seven patients were lost to follow-up for reasons unrelated to the study.

Modest but significant improvements in SARA scores (4.1; confidence interval [CI], 3.5 to 4.7; $P < 0.001$), ICARS (11; CI, 9.3 to 12.7; $P < 0.001$), CCASS (mean scores -7.0; CI, -10.4 to -3.5; $P < 0.001$), quality of life scores, motor cortex excitability, and cerebellar inhibition (0.24; CI, 0.19 to 0.30; $P < 0.001$) were observed in the treated group compared to sham stimulation at the end of the randomized, double-blind period. A greater

marginal benefit in motor scores was noted between the two groups at the end of the open-label period, suggesting an additive benefit after two treatments. The degree of improvement measured by SARA and ICARS was inversely correlated with disease duration (r_s =-0.37, P = 0.003), indicating that better clinical outcomes would be expected with earlier treatment. Significant clinical improvement was seen in both groups, regardless of etiology of cerebellar syndrome. Improvements in SARA score and cognitive scores correlated with the percentage of restoration in cerebellar inhibition measured by TMS (r_s = 0.42, P = 0.004 and r_s = 0.52, P < 0.001, respectively).

■ COMMENTARY

tDCS is a non-invasive, well-tolerated treatment that may confer motor and cognitive improvements. Findings in this study also suggest that repetitive treatments may confer modest longer-term symptomatic improvement if implemented earlier in the disease course.

One concern is limited access to treatment, since tDCS is only available at specialized centers and would require close follow-up by a movement specialist. Further study is needed to establish the benefit of tDCS in the treatment of cerebellar ataxia. ■

ABSTRACT & COMMENTARY

Is Pimavanserin Safe to Use in Patients with Parkinson's Disease?

By Andrea Lee, MD

Assistant Professor of Clinical Neurology and Assistant Attending Neurologist, New York-Presbyterian/Weill Cornell Medical College

SYNOPSIS: This retrospective cohort study of patients with Parkinson's disease ages 65 years or older residing in Medicare-certified long-term care facilities revealed pimavanserin use vs. nonuse is associated with an increased risk of 30-day hospitalization and higher 90-, 180-, and 365-day mortality.

SOURCE: Hwang YJ, Alexander GC, An H, et al. Risk of hospitalization and death associated with pimavanserin use in older adults with Parkinson disease. *Neurology* 2021;97:e1266-e1275.

This was a propensity score-based retrospective cohort study of pimavanserin users and nonusers with Parkinson's disease (PD). The authors accrued information on residents of Medicare-certified long-term care facilities between Nov. 1, 2015, and Dec. 31, 2018, using the Minimum Data Set (MDS) 3.0, which was linked with Medicare claims data. The MDS is a federally required clinical assessment of all individuals residing in Medicare-certified long-term care facilities. The clinical assessment is performed on admission to the long-term care facilities, periodically, and on discharge. The MDS contains information on long-term care residents' clinical, psychosocial, and functional characteristics.

The study cohort included long-term care residents 65 years of age and older diagnosed with PD. The authors defined the diagnosis of PD as ICD-10-CM diagnosis code G20 (PD) or receipt of a prescription for carbidopa or levodopa. From the cohort of long-term care residents with PD, those with a new outpatient prescription for pimavanserin from May 1, 2016, to Dec. 31, 2018, were accrued into the user group. After the index date for each pimavanserin user and 10 nonusers was identified, the following subjects were excluded: those without continuous enrollment in Medicare Parts A, B, and D for the six months prior to the index date, those without at least one MDS assessment in the six months prior to or one month after the index date, and those who were residing in skilled nursing facilities or hospitalized on the index date. After applying exclusion criteria, the final study cohort included 2,186 pimavanserin users and 18,212 nonusers.

The authors concluded that there was a higher risk of 30-day hospitalization with pimavanserin use vs. nonuse (inverse probabilities of treatment weights [IPTW]-adjusted hazard ratio [aHR], 1.24; 95% confidence interval [CI], 1.06-1.43). There was no association of pimavanserin use with 90-day hospitalization (aHR, 1.10; CI, 0.99-1.24) or with 30-day mortality (aHR, 0.76; CI, 0.56-1.03). Pimavanserin use vs. nonuse was associated with increased 90-day mortality (aHR, 1.20; CI, 1.02-1.41) that persisted after 180 days (aHR, 1.28; CI, 1.13-1.45) and one year (aHR, 1.56; CI ,1.42-1.72).

■ COMMENTARY

In PD, a variety of nonmotor symptoms are common. These include dementia and psychosis. In patients with long-term PD, as many as 80% experience dementia and as many as 60% experience psychosis. In PD, dementia is known to be associated with psychosis, and the use of antipsychotics for PD treatment is common. A study reported that, of newly diagnosed PD patients, approximately one-third were prescribed an antipsychotic within seven years, and another study reported a

six-year cumulative probability of initiating antipsychotic treatment at 50%.[1-3] Given that a previous study showed typical and atypical antipsychotics more than doubled mortality risk in patients with PD, the authors aimed to assess the risk of hospitalization and death associated with pimavanserin.[3]

Pimavanserin is a novel antipsychotic approved by the U.S. Food and Drug Administration (FDA) for the management of hallucinations and delusions in patients with PD. Pimavanserin blocks serotonin 5-HT2A receptors and does not have affinity for dopaminergic, histaminergic, muscarinic, or adrenergic receptors. Its lack of dopamine receptor affinity compared to typical or atypical antipsychotics (dopamine receptor affinity is well known to worsen motor symptoms of parkinsonism) makes it a particularly promising antipsychotic in this challenging patient population. Safety signals concerning a possible effect on mortality were observed previously in randomized and observational studies and spontaneous adverse event reporting of pimavanserin. A Phase III randomized trial of 199 patients reported serious adverse events in 11 (11%) patients in the pimavanserin group compared to 4 (4%) in the placebo group. The trend in deaths also was unfavorable, with two deaths in the pimavanserin group vs. one death in the placebo group. In the long-term open-label population, 11% of 497 patients treated with pimavanserin died, but no comparison group was available.

The results of this current study are important because of earlier signals of potential harm associated with pimavanserin, as well as continued uncertainty regarding its safety for the management of hallucinations and delusions in patients with PD. Although the FDA approved the use of pimavanserin among those with PD in 2016, it also published a black-box warning for increased risk of mortality in older adults with dementia, similar to other antipsychotics that have been used off-label in patients with PD and associated with increased risk of mortality.

This is the first cohort study that examined the risk of hospitalization and death associated with pimavanserin use compared to nonuse in older adults with PD, and the results may help to inform decisions about the risk/benefit balance of pimavanserin in clinical practice. While the study was not designed to assess the specific causes of the increased morbidity and mortality documented, prior work has found that the relationship between antipsychotics and risk of mortality may be driven by several factors, including higher rates of sudden cardiac death, acute myocardial infarction, acute kidney injury, pneumonia, falls, and fractures in older adults. Future studies may be warranted to elucidate the putative mechanisms for the risks of hospitalization and death associated with pimavanserin use. ■

REFERENCES

1. Marras C, Kopp A, Qiu F, et al. Antipsychotic use in older adults with Parkinson's disease. *Mov Disord* 2007;22:319-323.
2. Wang M-T, Lian P-W, Yeh C-B, et al. Incidence, prescription patterns, and determinants of antipsychotic use in patients with Parkinson's disease. *Mov Disord* 2011;26:1663-1669.
3. Weintraub D, Chiang C, Kim HM, et al. Association of antipsychotic use with mortality risk in patients with Parkinson disease. *JAMA Neurol* 2016;73:535-541.

ABSTRACT & COMMENTARY

Electrodiagnostic Findings in Thoracic Outlet Syndrome

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: The diagnosis of thoracic outlet syndrome may be difficult and relies on specific clinical, imaging, vascular, and electrodiagnostic features. None of the currently recommended treatments have been shown to be effective, but there are few randomized clinical treatment trials.

SOURCE: Mul K, Pesser N, Vervaart K, et al. Variability in electrodiagnostic findings associated with neurogenic thoracic outlet syndrome. *Muscle Nerve* 2021; Aug 11. doi: 10.1002/mus.27395. [Online ahead of print].

Thoracic outlet syndrome (TOS) is a controversial entity, and a confusing term, encompassing a group of neurological and vascular disorders related to compression of the neurovascular bundle above the first rib and behind the clavicle. This may give rise to a constellation of symptoms from arterial compression, from venous compression, and some from peripheral nerve compression.

Adding to the confusion, multiple terms have been applied to TOS, including cervical rib syndrome, costoclavicular syndrome, scalenus anticus syndrome, hyperabduction syndrome, subcoracoid-pectoralis minor syndrome, and Gilliatt-Sumner hand. True neurogenic TOS (NTOS) is diagnosed when clearly defined weakness and sensory loss in the arm and hand are present, resulting from an anomalous fibrous band or accessory

cervical rib over which the lower trunk of the brachial plexus is angulated and stretched. What are the electrodiagnostic correlates associated with TOS?

Databases from tertiary referral clinics of the Neurology Department of the Radboud University Medical Center, Nijmegen, Netherlands, and the TOS-Expert Center of the Catharina Hospital, Eindhoven, Netherlands, were searched for patients diagnosed with NTOS between 2010 and 2021 who had undergone imaging of the thoracic outlet and electrodiagnostic studies (EMG). Inclusion criteria included symptoms or signs of lower cervical root or lower trunk brachial plexus involvement, imaging studies or intra-operative confirmation documenting compression of the lower plexus, and upper extremity EMG that were abnormal to any degree. Patients with a history of trauma or injury to the brachial plexus, or upper limb radiculopathy or mononeuropathy, were excluded. Brachial plexus imaging was performed using nerve ultrasound and/or magnetic resonance imaging, and NTOS was confirmed when enlargement of the lower trunk was documented.

Fourteen patients with NTOS fulfilled entry criteria, all of whom had lower brachial plexus compression documented and confirmed by imaging studies, and EMG which were abnormal. An axonal pattern consistent with T1 radiculopathy more than C8 nerve fiber involvement was present in seven patients, with the remainder having a variety of presentations, including C8 more than T1 involvement, equal involvement of C8 and T1, pure motor findings with normal sensory nerve action potential responses (SNAPs), needle EMG abnormalities limited to the flexor carpi radialis and biceps brachii muscles, and a single patient with an abnormal median SNAP from the third digit. Patterns of EMG abnormalities other than the "classic" T1 > C8 root pattern should not deter a diagnosis of TOS. High-resolution nerve imaging is a necessary complement in the evaluation of these patients.

■ COMMENTARY

TOS has a reported incidence of anywhere from three to 80 per 1,000 population and is more common between adolescence and middle age, particularly in females between 20 and 50 years of age. Treatment includes conservative measures as the first line, including physical therapy, lifestyle modification, and nonsteroidal anti-inflammatory agents. Botulinum toxin A injection of the anterior or middle scalene muscle, or of the scalene minimus muscle if present, has been suggested, but a randomized, double-blind, controlled trial demonstrated no improvement of pain or symptom reduction.

Paradoxically, the treated group experienced longer duration of symptoms than the control group, six vs. three years, respectively. Combined injection of steroids and local anesthetics have been beneficial, improving

DocuSign Envelope ID: A73BF226-B07D-4BCA-AF59-DFAB60CC1567

UNITED STATES POSTAL SERVICE®

Statement of Ownership, Management, and Circulation (All Periodicals Publications Except Requester Publications)

1. Publication Title	2. Publication Number	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 3 4	10/1/2021
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$299

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)* — Contact Person: Sabrina Johnson; (919) 459-9495

1010 Sync St., Ste.100, Morrisville, NC 27560-5468.

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*

1010 Sync St., Ste.100, Morrisville, NC 27560-5468.

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*

Relias LLC, 1010 Sync St., Ste.100, Morrisville, NC 27560-5468.

Editor *(Name and complete mailing address)*

Jason Schneider

Managing Editor *(Name and complete mailing address)*

Leslie Coplin

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Relias LLC	1010 Sync St., Ste.100, Morrisville, NC 27560-5468.
Bertelsmann Learning LLC	1745 Broadway, New York, NY 10019

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☑ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, July 2014 *[Page 1 of 4 (see instructions page 4)]* PSN: 7530-01-000-9931 **PRIVACY NOTICE:** See our privacy policy on *www.usps.com*.

DocuSign Envelope ID: A73BF226-B07D-4BCA-AF59-DFAB60CC1567

13. Publication Title

14. Issue Date for Circulation Data Below: September 2021

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*			155	142
b. Paid Circulation *(By Mail and Outside the Mail)*	(1)	Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	130	121
	(2)	Mailed In-County Paid Subscriptions Stated on PS Form 3541 *(Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)*	0	0
	(3)	Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS®	4	2
	(4)	Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®)	6	4
c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]* ▶			140	127
d. Free or Nominal Rate Distribution *(By Mail and Outside the Mail)*	(1)	Free or Nominal Rate Outside-County Copies included on PS Form 3541	0	0
	(2)	Free or Nominal Rate In-County Copies Included on PS Form 3541	0	0
	(3)	Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail)	0	0
	(4)	Free or Nominal Rate Distribution Outside the Mail *(Carriers or other means)*	2	2
e. Total Free or Nominal Rate Distribution *(Sum of 15d (1), (2), (3) and (4))*			2	2
f. Total Distribution *(Sum of 15c and 15e)* ▶			142	129
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))* ▶			13	13
h. Total *(Sum of 15f and g)*			155	142
i. Percent Paid *(15c divided by 15f times 100)* ▶			99%	99%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

DocuSign Envelope ID: A73BF226-B07D-4BCA-AF59-DFAB60CC1567

UNITED STATES POSTAL SERVICE®

Statement of Ownership, Management, and Circulation (All Periodicals Publications Except Requester Publications)

16. Electronic Copy Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Paid Electronic Copies ▶		
b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a) ▶		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a) ▶		
d. Percent Paid (Both Print & Electronic Copies) (16b divided by 16c × 100) ▶		

☐ **I certify that 50% of all my distributed copies (electronic and print) are paid above a nominal price.**

17. Publication of Statement of Ownership

☑ If the publication is a general publication, publication of this statement is required. Will be printed in the November issue of this publication. ☐ Publication not required.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date

DocuSigned by: kay krafft 4007404A3CFE4A6E... — Chief Executive Officer — 29-Sep-2021

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

symptoms and overall function, with surgical decompression considered in the 30% to 40% in whom these measures fail.[1] ■

REFERENCE

1. Li N, Dierks G, Vervaeke HE, et al. Thoracic outlet syndrome: A narrative review. *J Clin Med* 2021;10:962.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to ReliasMedia.com and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be directed automatically to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. **Which of the following are true of transcranial direct current stimulation (tDCS) treatment?**
   a. It results in short-term improvement in motor scores.
   b. It results in short-term improvement in cognitive function.
   c. It results in restoration of cerebellar inhibition.
   d. All of the above.

2. **Based on the current package insert warnings, which of the following antiseizure medications are *not* associated with increased suicidal risk?**
   a. Everolimus and fenfluramine
   b. Lacosamide, ezogabine, and clobazam
   c. Eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate
   d. None of the above

3. **Which of the following describes the mechanism of action of atogepant in migraine prevention?**
   a. Small molecule calcitonin gene-related peptide (CGRP) receptor agonist
   b. Small molecule CGRP receptor antagonist
   c. Human monoclonal antibody that binds to the CGRP ligand
   d. Human monoclonal antibody that binds to the CGRP receptor

4. **The use of antipsychotic medications in elderly people with Parkinson's disease (PD) may result in which of the following consequences?**
   a. Improvement in cognitive function in those with dementia
   b. Reduction in the tremor of PD
   c. Increased risk of hospitalization and death
   d. Improvement in gait

5. **Which of the following patterns of electrodiagnostic findings is *not* consistent with thoracic outlet syndrome?**
   a. T1 more so than C8 nerve fiber involvement
   b. C8 more so than T1 nerve fiber involvement
   c. Equal nerve fiber involvement of C8 and T1
   d. Equal nerve fiber involvement of C6 and C7