PracticalNeurology® NEWS

SPECIAL REPORT

2018 Drug and Device Approvals for Neurology

HEADACHE & PAIN

Noninvasive Vagus Nerve Stimulation (Gammacore; electroCore, Basking Ridge, NJ)

Cleared: November 28, 2018 and January 29, 2018
Indications: adjunctive preventive treatment for adults with cluster headache and treatment of adults with migraine.
Available as: self-administered 2-minute doses of electric stimulation supplied in a hand-held device to be given twice daily, upon awakening and again 7-10 hours later for prevention of cluster headache, or once upon experiencing migraine pain.

Noninvasive vagus nerve stimulation (nVNS) has been approved previously for acute treatment of migraine and episodic cluster headache, it is now the only Food and Drug Administration (FDA)-cleared adjunctive preventive treatment for adults with cluster headache. Intention-to-treat (ITT) patients who received the standard of care and gammaCore (n = 45) during a randomized trial phase had a greater reduction from the baseline (−5.9) in the number of weekly cluster attacks than those receiving standard of care (−2.1; n = 48), for a mean therapeutic gain of 3.9 fewer cluster attacks per week (P = .02). In a site-adjusted model, the mean therapeutic gain was 4.2 fewer attacks per week (P = .02). Of patients treated with nVNS, 40% experienced more than a 50% reduction in cluster attacks per week and had a 57% reduction in use of rescue medications compared with 8.3% and 0.0%, respectively, of patients given sham treatment (P < .001).

Approval for treatment of migraine was based upon data showing nVNS was superior to sham in aborting the first treated migraine at 30 and 60 minutes. Repeated-measures test validated the superiority of nVNS over sham through 120 minutes. Other significant benefits of nVNS included mild or no pain at 120 minutes, changes in pain intensity from baseline to 60 and 120 minutes, and ≥50% responder (pain free and mild/pain free) rates at 120 minutes.

Sufentanil (Dsuvia; AcelRx, Redwood City, CA)

Approved: November 2, 2018
Indication: treatment of severe pain in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments.
Available as: 30 mcg sufentanil tablet in a single-dose, prefilled applicator for sublingual administration.
In a randomized, double-blind, placebo-controlled trial, adults with postoperative pain treated with sublingual sufentanil (30 mcg) had a statistically larger reduction from baseline in summed pain intensity difference over a period of 12 hours compared to those treated with placebo. Difference in pain intensity occurred within 15 minutes of treatment and meaningful pain relief was seen after 1 dose. Only 22% of patients treated needed rescue treatment with morphine compared with 65% of patients who received placebo. Sublingual administration is a useful option for patients with a nil-by-mouth (NPO) status or difficult venous access.

Smartphone Application (myPTM; Medtronic, Minneapolis, MN)

Approved: October 24, 2018
Indication: physician-limited self-administration of drug dose for patient implanted with an intrathecal drug-delivery pump (SynchroMed II; Medtronic, Minneapolis, MN).
Available as: a smart phone application that can be programmed by the physician and used by the patient.

Physicians can program a device with preset limits; patients then use the app for dose delivery to the intrathecal space within those limits. Intrathecal drug delivery reduces the dose needed for effective pain relief and can reduce use of oral opioids. Features of the application include information about the therapy being given, clear controls for self-delivery of a bolus as prescribed, alerts when requests for boluses exceed physician-set dose limits, and the ability for physicians to track medication usage. It is hoped that this patient-centered approach will increase patient-physician partnership in the control of a patient's chronic pain.

Galcanezumab-glnm (Emgality; Lilly, Indianapolis, IN)

Approved: September 26, 2018
Indication: prevention of chronic migraine in adults.
Available as: a self-administered subcutaneous injection

(120 mg) with recommended loading dose of 240 mg (2 consecutive subcutaneous injections of 120 mg each), followed by monthly maintenance 120 mg doses.

Galcanezumab-glnm is a calcitonin gene-related peptide (CGRP) antagonist indicated for the preventive treatment of migraine in adults. In clinical trials, patients with chronic migraine were treated with galcanezumab-glnm had a mean change of -4.8 MHD/month compared to -2.7 for those given placebo ($P < .001$). At least a 50% reduction in MHD in a given month occurred in 28% of patients treated compared with 15% of those given placebo ($P < .001$). The most common adverse reactions were injection site reactions.

Fremanezumab-vfrm (Ajovy; Teva Pharmaceuticals, North Wales, PA)

Approved: September 14, 2018
Indication: prevention of chronic migraine in adults.
Available as: subcutaneous injections of 225 mg given once per month OR every 3 months (3 injections for 675 mg).

Fremanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand to block binding to the CGRP receptor. Approval was based on data from 2 phase 3 clinical trials that showed treatment with fremanezumab significantly reduced patients' number of migraine days per month compared to placebo ($P < .001$) and increased the number of patients who had a 50% or more reduction in headache days permonth compared to placebo ($P < .001$). Treatment with fremanezumab significantly reduced the number of days per month patients needed acute headache treatment and reduced disability as measured by the migraine disability assessment score (MIDAS).

Erenumab-aooe (Aimovig; Novartis, East Hanover, NJ)

Approved: May 18, 2018
Indication: prevention of migraine in adults.
Available as: autoinjectable intramuscular injection of 70 mg.

Erenumab-aooe is a monoclonal antibody that blocks the CGRP receptor. In a phase 3 trial, erenumab reduced treated patients' monthly headache days by 1.4 (70 mg dose) and 1.9 (140 mg dose) compared to placebo. Efficacy, tolerability, and safety was assessed in more than 3,000 patients for up to 5 years.

The most common adverse reactions are injection site reactions and constipation.

Lidocaine Patch 1.8% (Ztlldo, Sorrento Pharmaceuticals, San Diego, CA)

Approved: February 28, 2018
Indication: treatment of adults with postherpetic neuralgia.
Available as: single-dose topical system containing 1.8% lidocaine that can be cut into smaller pieces.

Designed to achieve superior adhesion and drug delivery efficiency, this lidocaine patch achieves pain control with 36 mg/patch. Safety and efficacy was comparable to other available lidocaine patches that require higher doses. Pharmacokinetic studies demonstrated bioequivalence between this new patch and others already available. Lack of adhesion is one of the most common reasons for nonadherence to treatment with lidocaine patches, making the better adhesion particularly useful for patients.

Spinal Cord Stimulation (Precision System; Boston Scientific, Valencia, CA)

Cleared: January 11, 2018.
Indication: treatment of adults with chronic or intractable pain of trunk and/or limbs.
Available as: an implantable, programmable device for delivery of electric current (neurostimulation) to the spinal cord.

A total of 116 patients had the system implanted and 3,166 device-months of experience was considered in a retrospective clinical evaluation. All patients had chronic pain of the trunk and/or limbs including unilateral or bilateral pain associated with failed back surgery syndrome or intractable low back and leg pain. In this study, 25% of patients with the system had more than a 50% reduction in their pain rating. Of those who had this level of efficacy, 89% had continued efficacy of 50% or more reduction in pain over a follow up period of 34 months.

Spinal Cord Stimulation (Senza II System; Nevro, Redwood City, CA)

Cleared: January 4, 2018.
Indication: treatment of adults with chronic or intractable pain of trunk and/or limbs.
Available as: an implantable, programmable device for delivery of electric current (neurostimulation) to the spinal cord.

This second-generation model of a previously-approved device for is smaller than the first-generation device with the same safety and efficacy.

TABLE. 2018 DRUG AND DEVICE APPROVALS FOR PATIENTS WITH HEADACHE OR PAIN

Drug (Trade Name, Manufacturer)	Approval/ Clearance	Indication(s)	Available as
Noninvasive vagus nerve stimulation (Gammacore device; electroCore, Basking Ridge, NJ)	Nov. 28	Adjunctive preventive treatment of cluster headache in adults	Hand-held device
Sufentanil (Dsuvia; AcelRx, Redwood City, CA)	Nov. 2	Treatment of adults with severe pain in certified medical centers	Sublingual tablet
Galcanezumab-gnlm (Emgality; Lilly, Indianpolis, IN)	Sept. 26	Prevention of chronic migraine in adults	Subcutaneous injection
Fremanezumab (Ajovy; Teva Pharmaceuticals, North Wales, PA)	Sept. 14	Prevention of chronic migraine in adults	Subcutaneous injection
Erenumab-aooe (Aimovig; Novartis, East Hanover, NJ)	May 18	Prevention of chronic migraine in adults	Intramuscular autoinjection
Lidocaine patch (ZTLido; Sorrento Pharmaceuticals, San Diego, CA)	Feb. 28	Treatment of pain associated with postherpetic neuralgia in adults	Single-dose topical system
Noninvasive vagus nerve stimulation (Gammacore device; electroCore, Basking Ridge, NJ)	Jan. 23	Treatment of adults with migraine	Hand-held device
Smart phone application for use with intrathecal drug delivery system (myPTM; Medtronic, Minneapolis, MN)	Oct. 24	Adults implanted with an intrathecal drug delivery pump (SynchroMed II; Medtronic, Minneapolis, MN)	Smart phone application
Spinal cord stimulation (Precision system; Boston Scientific, Valencia, CA)	Jan. 11	Treatment of adults with chronic or intractable pain of trunk and/or limbs	Surgically implantable device
Spinal cord stimulation (Senza II device; Nevro, Redwood City, CA)	Jan. 4	Treatment of adults with chronic or intractable pain of trunk and/or limbs	Surgically implantable device

EPILEPSY

Clobazam Oral Film (Sympazan; Aquestive Therapeutics, Warren, NJ)

Approved: November 1, 2018
Indication: Adjunctive treatment of patients with Lennox-Gastaut syndrome.
Available as: oral film in doses of 5 mg, 10 mg, 20 mg.

The approval of this new formulation of clobazam was based upon pharmacokinetic studies of bioequivalence to previously approved formulations. For a drug formulation to be considered of average bioequivalence to a previously approved drug by the FDA, there must be a 90% CI that pharmacokinetic measures fall within 80% to 125% of the same measures for the dose originally approved. The oral film formulation met a more rigorous standard with all measures falling between 90 and 110%, supporting that the oral film formulation is providing a dose that is consistent and may be easier to administer without needing to crush tablets, swallow pills with water, or use a cup.

Stiripentol (Diacomit; Biocodex, Redwood City, CA)

Approved: August 20, 2018
Indication: treatment of patients, age at least 2 years, with seizures associated with Dravet syndrome, who are taking clobazam.
Available as: powder for oral suspension or capsules of 250 mg or 500 mg to be given in dose of 50mg/kg/day in 2-3 divided doses up to a maximum of 3,300 mg /day.

In 2 clinical trials, 71% (n = 41; *P* = .0003) and 67% (n = 23; *P* = .0006) of patients taking stiripentol as adjunctive treatment had at least a 50% reduction in seizure frequency from baseline compared to 5% and 9%, respectively, of patients given placebo.

A total of 43% and 25% of patients in the 2 trials, respectively, reported no generalized clonic or tonic-clonic seizure (ie, 100 % reduction) for the duration of the study that was not seen in any patients given placebo.

Midazolam Injection (Seizalam; Meridian Medical Technologies, Columbia, MD)

Approved September 14, 2018
Indication: treatment of adults experiencing status epilepticus.
Available as: a multidose syringe containing 50 mg (5 mg/mL) of midazolam for intramuscular injection of a 10 mg dose.

This is a new indication for a drug previously approved as a perioperative sedative and long-used off-label for treatment of status epilepticus, for which it is now approved. The data leading to approval came from the RAMPART study (NCT00809146) in which 73% (n = 448; *P* = .002) of patients who received intramuscular midazolam for prehospital treatment of status epilepticus had seizures stop before arriving at the hospital compared with 63.4% (n = 445) of patients who received intravenous lorazepam. For patients still in status epilepticus on arrival, midazolam administration was noninferior to intravenous lorazepam.

Cannabidiol (Epidiolex; GW Pharma, Carlsbad, CA)

Approved: June 25, 2018
Indication: For treatment of adult patients with medically refractory partial-onset seizures.
Available as: oral solution of 100 mg/mL to be given as a starting dose of 2.5 mg/kg twice daily (5mg/kg/day) and titrated to a maintenance dose of 10 mg/kg twice daily (20 mg/kg/day).

A first-in-class treatment for epilepsy and also the first FDA-approved derivative of *Cannabis sativa*, more commonly known as marijuana and resclassified by the Drug Enforcement Agency (DEA) as a Schedule 5 substance. In clinical trials, CBD significantly reduced the frequency of drop seizures in patients with Lennox-Gastaut syndrome by as much as 41.9% compared to a 17.2% drop with placebo and decreased seizure frequency by 39% in patients with Dravet syndrome compared to a 13% decrease in patients treated with placebo. The FDA-approved CBD contains less than 0.01% of tetrahydrocannabinol (THC) and does not produce the euphoria or "high" of marijuana or THC. It is a pharmaceutical-grade formulation that patients can reliably use without concerns of psychoactive effects, addiction disorders, or safety concerns associated with uncontrolled products.

Deep Brain Stimulation (Medtronic DBS System; Medtronic, Minneapolis, MN)

Cleared: May 1, 2018
Indication: For treatment of adult patients with medically refractory partial-onset seizures.
Available as: an implantable, programmable device for delivery of electric current (neurostimulation) to the anterior nucleus of the thalamus.

The SANTE trial (NCT00101933) showed that baseline seizure frequency was reduced by 40.4% when patients had implanted deep brain stimulation of the anterior thalamic nucleus compared with 14.5% in those given sham stimulation during a 3-month controlled blinded period. In the 7-year, open-label extension portion of the study, all patients (n = 110) received deep brain stimulation and had a median 75% reduction in seizure frequency compared with baseline.

TABLE. 2018 DRUG AND DEVICE APPROVALS FOR PATIENTS WITH EPILEPSY

Drug, (Trade Name, Manufacturer)	Approval/ Clearance	Indication(s)	Available as
Clobazam (Sympazam; Aquestive Therapeutics, Warren, NJ)	Nov. 1	Adjunctive treatment of patients ≥ 2 yrs for seizures associated with Lennox-Gastaut syndrome	Oral film
Midazolam (Seizalam; Meridian Medical Technologies, Columbia, MD)	Sept. 14	Treatment of adults with status epilepticus	Intramuscular injection
Stiripentol (Diacomit; Biocodex, Redwood City, CA)	Aug. 20	Adjunctive treatment of patients, ≥ 2 yrswho are also taking clobazam, for seizures associated with Dravet syndrome	Powder for oral suspension or capsules
Cannabidiol (Epidiolex, GW Pharma, Carlsbad, CA)	June 25	Adjunctive treatment of patients age 2 and up with seizures associated with either Lennox Gastaut-syndrome or Dravet syndrome	Oral solution
Deep brain stimulation (Medtronic DBS system; Medtronic, Minneapolis, MN)	May 1	Medically refractory partial onset seizures	Surgically implantable device

MOVEMENT DISORDERS

MRI-Guided Focused Ultrasound (Exablate; Insightec, Miami, FL)

Approved: December 19, 2018
Indication: treatment of adults with tremor-dominant Parkinson's disease
Available as: incisionless neurosurgical thalamotomy.

Previously approved for the treatment of adults with essential tremor, the indication for use was expanded to include patients with tremor-dominant Parkinson's disease.

Amantadine Extended Release (Osmolex; Osmotica, Marietta, GA)

Approved: February 16, 2018
Indication: treatment of adults with Parkinson's disease or drug-induced extrapyramidal symptoms.
Available as: 129 mg, 193 mg, and 258 mg tablets to be taken once daily, in the morning. Maximum daily dose is 322 mg.

This extended release formulation of amantadine is taken once daily in the morning and releases amantadine throughout the day. In clinical trials it was shown to be as safe and effective as immediate-release amantadine.

TABLE. 2018 DRUG AND DEVICE APPROVALS FOR PATIENTS WITH MOVEMENT DISORDERS

Drug, (Trade Name, Manufacturer)	Approval/ Clearance	Indication(s)	Available as
MRI-guided focused ultrasound (Exablate; Insightec, Miami, FL)	Dec. 19	Treatment of adults with tremor-dominant Parkinson's disease	Incisionless neurosurgical procedure
Amantadine extended release (Osmolex; Osmotica, Marietta, GA)	Feb. 16	Treatment of adults with Parkinson's disease or drug-induced extrapyramidal reactions	Tablets

NEUROMUSCULAR DISORDERS

Amifampridine (Firdapse; Catalyst Pharmaceuticals, Coral Gables, FL)

Approved: November 28, 2018
Indication: treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.
Available as: 10 mg tablets, prescored. Starting dose 15 mg per day, which can be increased 5 mg per day every 3 to 4 days to maximum dose of 80 mg/day in maximum single 20 mg doses.

Patients treated with amifampridine had less decline from baseline in the Quantitative Myasthenia Gravis (QMG) score and the Subject Global Impression (SGI) score compared with patients given placebo (P =.02). Although the QMG scores for both groups declined during the 14-day period, there was significantly more worsening in patients given placebo (P = .003).

Inotersen (Tegsedi; Akcea Therapeutics, Boston, MA and Ionis Pharmaceuticals, Carlsbad, CA)

Approved: October 5, 2018
Indication: treatment of adults with polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis.
Available as: prefilled syringe containing 284 mg per 1.5 mL to be given weekly.

Inotersen is an RNA-interference therapy and patients (n = 112) treated with inotersen had significant improvements in neuropathy and quality of life measures compared to those treated with placebo (n = 60). In an open-label extension study, patients were followed for up to 66 months and 47% of patients improved or stabilized their neurologic function (P = .0005), muscle weakness (P < .001), reflexes (P = .04), sensory component (P < .001), heat conduction (P = .025), and heat-pain (P = .001). In the open-label extension trial, the key safety findings of thrombocytopenia and renal events were consistent with that seen in the placebo-controlled study and were monitorable and manageable.

Patisiran (Onpattro; Alnylam Pharmaceuticals, Cambridge, MA)

Approved: August 28, 2018.
Indication: treatment of adults with polyneuropathy of hATTR amyloidosis.
Available as: infusion of lipid complex in a single-dose vial for infusion over 80 minutes. Recommended dose is 0.3 mg/kg every 3 weeks (if patient >100 kg, dose is 30 mg).

In clinical trials, 225 patients with hATTR amyloidosis with neuropathy were randomly assigned to receive

0.3 mg/kg of patisiran (n = 148) or placebo (n = 77). Patients treated with patisiran had significant improvements in neuropathy, gait speed, and modified body-mass index compared to those treated with placebo. At 18 months, patients treated with patisiran had least-squares mean R-ODS scores that were 9 points lower than the mean score of patients given placebo ($P = 4.07x10^{-16}$). Patients treated with patisiran had less difficulty reading a newspaper or book (31%) or standing for a long period of time (54%) compared to those given placebo (53% and 80%, respectively).

TABLE. 2018 DRUG APPROVALS FOR PATIENTS WITH NEUROMUSCULAR DISEASE

Drug (Trade Name, Manufacturer)	Approval	Indication(s)	Available as
Amifampridine (Firdapse; Catalyst Pharmaceuticals, Coral Gables, FL)	Nov. 28	Treatment of adults with Lambert-Eaton myasthenic syndrome	Tablets
Inotersen (Tegsedi; Akcea Therapeutics, Boston, MA and Ionis Pharmaceuticals, Carlsbad, CA)	Oct. 5	Treatment of adults with polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis	Subcutaneous injection
Patisiran (Onpattro; Alnylam Pharmaceuticals, Cambridge, MA)	Aug 28	Treatment of adults with polyneuropathy of hATTR amyloidosis	Intravenous infusion

STROKE

Carotid Stent (Gore Carotid Stent; Gore, Flagstaff, AZ)

Approved: November 1, 2018
Indication: treatment of adults with contraindications to carotid endarterectomy and at least 80% occlusion of the carotid artery or who have had a recent stroke and have at least 50% occlusion of the carotid artery.
Available as: nickel-titanium alloy (nitinol) tubing, laser-cut into mesh shape, with expanded polytetrafluoroethylene (ePTFE) lattice on outer surface, mounted on delivery catheter.

Of 244 patients treated with this stent and followed for 1 year, 94% had no major adverse events (ie, death, any stroke, myocardial infarction [MI]) in the first month, or ipsilateral stroke in months 2-12). Of the major adverse events, 4 were myocardial infarction, 3 were a major stroke, 3 had ipsilateral stroke in months 2 to 12, and 1 patient died from pulseless electrical activity at day 15. Of the ipsilateral stroke, all were minor ischemic strokes that occurred at day 50, day 249, and day 276. The 95.1% 1-sided upper confidence limit was 8.5%, significantly less than the 16.9% performance goal ($P < .00001$) indicating this stent is durable for at least 1 year.

Flow-Diverting Stent (Surpass Streamline Diverter; Stryker Neurovascular, Fremont, CA)

Approved: July 13, 2018
Indication: treatment of adults with wide-neck carotid aneurysms (> 4 mm or with dome-to-neck ratio < 2 mm) or fusiform intracranial aneurysms (diameter 2.5-5.3 mm).
Available as: a cobalt chromium and platinum tungsten braided, self-expandable tube.

In a clinical study of 180 subjects included in the primary analysis, 62.8% who were treated with the diverter achieved a successful treatment (complete occlusion) of their intracranial aneurysm within 1-year postprocedure without retreatment or clinically significant in-stent stenosis. ■

TABLE. 2018 DEVICE APPROVALS FOR PATIENTS WITH CEREBROVASCULAR DISORDERS

Device (Trade Name, Manufacturer)	Clearance	Indication(s)	Available as
Carotid stent (Gore carotid stent; Gore, Flagstaff, AZ)	Nov. 1	Treatment of adults with carotid artery stenosis who have contraindications to endarterectomy	Stent on delivery catheter
Flow-diverting stent (Surpass streamline diverter; Stryker Neurovascular, Fremont, CA)	July 13	Treatment of adults with wide-neck or fusiform carotid artery aneurysm	A cobalt chromium and platinum tungsten braided, self-expandable tube