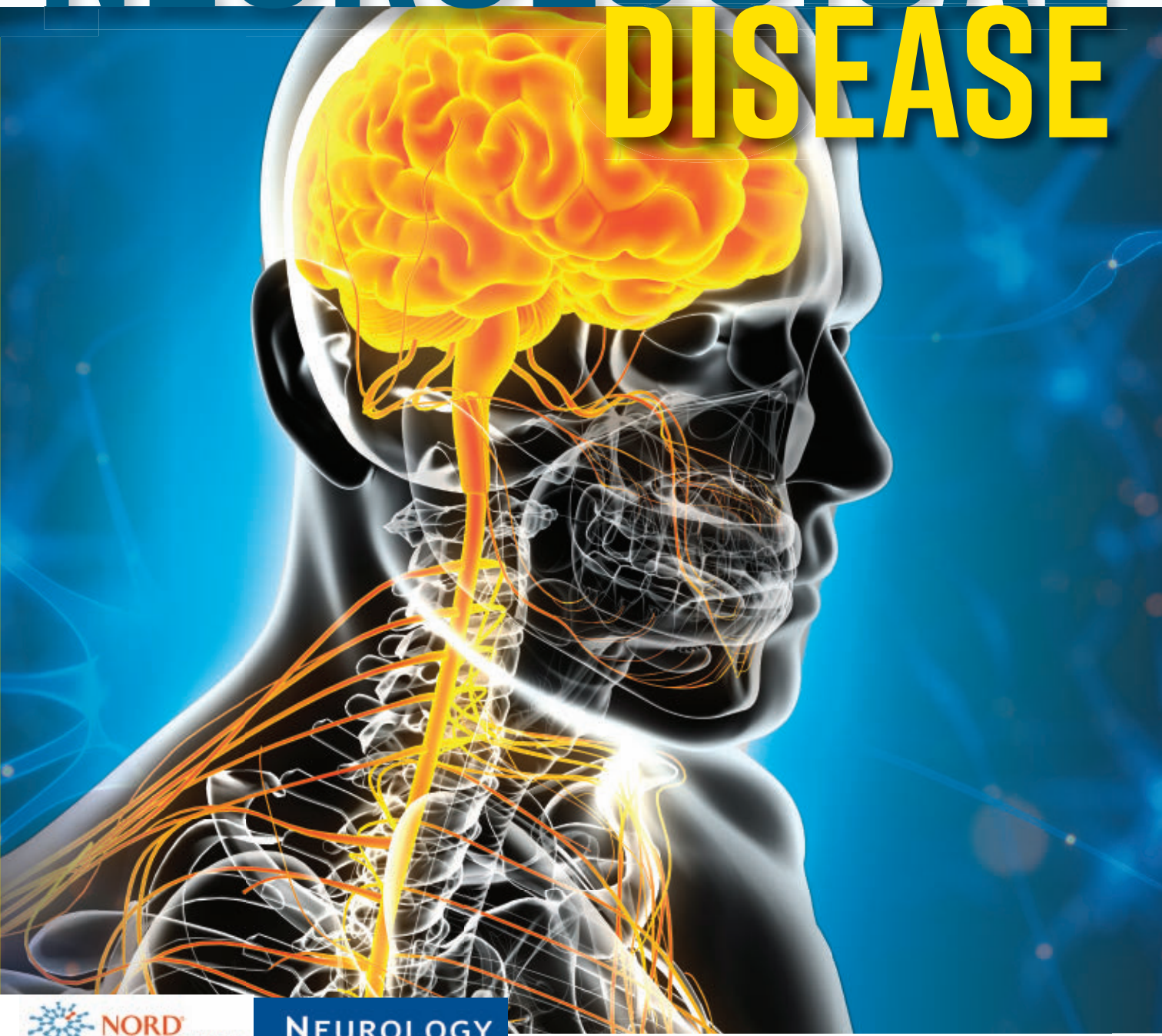
MARCH 2018

SPECIAL REPORT

RARE NEUROLOGICAL DISEASE



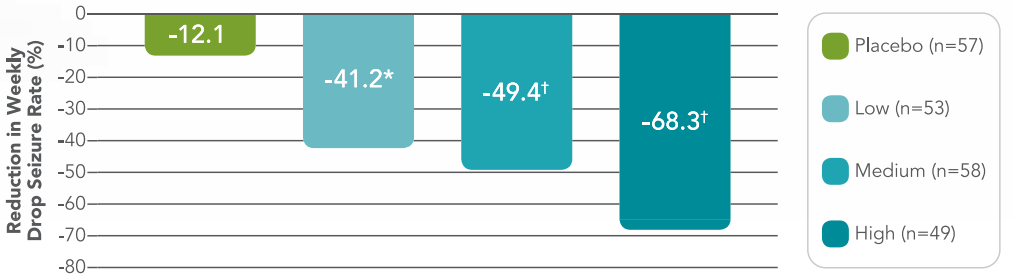
NORD National Organization for Rare Disorders

NEUROLOGY REVIEWS

A SUPPLEMENT TO *NEUROLOGY REVIEWS*

SELECTED ARTICLES

Reductions in Mean Weekly Rate of Drop Seizures by Dose (N=217, mITT)[1,2]



*P<0.05, †P<0.01. mITT = modified intent-to-treat.

Study Design: CONTAIN (**C**l**O**bazam in Patie**NT**s with Lennox-G**A**staut Sy**N**drome) was a randomized, double-blind, placebo-controlled study consisting of a 4-week baseline period followed by a 3-week titration period and a 12-week maintenance period (N=238, randomized). Patients aged 2 to 54 years with a current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30 kg), and then randomized to placebo or 1 of 3 target maintenance doses of ONFI. The dosage groups were placebo (n=59); low-dose (5 mg/10 mg, n=58); medium-dose (10 mg/20 mg, n=62); and high-dose (20 mg/40 mg, n=59). Doses above 5 mg/day were administered in 2 divided doses. The primary endpoint was the percentage reduction in mean weekly rate of drop seizures (atonic, tonic, or myoclonic) from the 4-week baseline period to the 12-week maintenance period.

- In the CONTAIN trial, drop seizures were defined as drop attacks or spells that involved the entire body, trunk, or head, and[2]:
  - Led to a fall or injury, slumping in a chair, or hitting the head on a surface
  - Could have led to a fall or injury, depending on the position of the patient at the time of the attack or spell
- Patients in the trial experienced ≥2 drop seizures (atonic, tonic, or myoclonic) per week during 4-week baseline, while receiving stable doses of 1 to 3 AEDs ≥30 days prior to screening[2]

References: 1. ONFI [package insert]. Deerfield, IL: Lundbeck. **2.** Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology.* 2011;77(15):1473-1481.

Onfi®
(clobazam)CV
10 mg, 20 mg Tablets
2.5 mg/mL Oral Suspension

A FORCE FOR REDUCTION

Indications and Usage

ONFI® (clobazam)℞ is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

Important Safety Information

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
See full Prescribing Information for complete boxed warning.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Contraindication: Hypersensitivity
ONFI is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Hypersensitivity reactions have included serious dermatological reactions.

Risks from Concomitant Use with Opioids (see Boxed Warning)
Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe ONFI concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. Advise both patients and caregivers about the risks of respiratory depression and sedation when ONFI is used with opioids.

Potentiation of Sedation from Concomitant Use with Central Nervous System (CNS) Depressants
ONFI has a CNS depressant effect. Caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol and that the effects of other CNS depressant drugs or alcohol may be potentiated.

Somnolence or Sedation
ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation was reported at all effective doses and was dose-related. In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Monitor patients for somnolence and sedation, particularly with concomitant use of other CNS depressants. Caution patients against engaging in hazardous activities that require mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of ONFI is known.

Withdrawal Symptoms
As with all antiepileptic drugs (AEDs), withdraw ONFI gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. Withdrawal symptoms occurred following abrupt discontinuation of ONFI; the risk of withdrawal symptoms is greater with higher doses.

Serious Dermatological Reactions
Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with ONFI in both children and adults during the post-marketing period. Discontinue ONFI at the first sign of rash, unless the rash is clearly not drug-related.

Physical and Psychological Dependence
Carefully monitor patients with a history of substance abuse when receiving ONFI or other psychotropic agents because of the predisposition of such patients to habituation and dependence. In clinical trials, cases of dependency were reported following abrupt discontinuation of ONFI. The risk of dependence increases with increasing dose and duration of treatment.

Suicidal Behavior and Ideation
AEDs, including ONFI, increase the risk of suicidal thoughts or behavior in patients. Inform patients, their caregivers, and families of the risk and advise them to monitor and report any emergence or worsening of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. If these symptoms occur, consider whether it may be related to the AED or illness, because epilepsy itself can increase these risks.

Pregnancy, Registry and Nursing Mothers

- Based on animal data, ONFI may cause fetal harm and should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
  - Encourage patients to call the toll-free number 1-888-233-2334 to enroll in the Pregnancy Registry or visit http://www.aedpregnancyregistry.org/.
- ONFI is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ONFI, discontinue nursing or discontinue the drug.

Adverse Reactions
The most commonly observed adverse reactions reported in an LGS randomized, double-blind, placebo-controlled, parallel group clinical trial of patients who received clobazam as adjunctive therapy (≥10% in any treatment group and at least 5% greater than placebo, respectively) were somnolence or sedation (32% vs. 15%), somnolence (25% vs. 12%), pyrexia (17% vs. 3%), lethargy (15% vs. 5%), aggression (14% vs. 5%), drooling (14% vs. 3%), irritability (11% vs. 5%), ataxia (10% vs. 3%), and constipation (10% vs. 0%).

Please see Brief Summary of Prescribing Information, including Boxed Warning for risks from concomitant use with opioids, on the following pages. For full Prescribing Information, Medication Guide, and Instructions for Use, go to ONFI.com for more information.

Lundbeck Your Partner in Epilepsy™

ONFI® (clobazam) tablets, for oral use, CIV
ONFI® (clobazam) oral suspension, CIV
Brief Summary of Prescribing Information
(See package insert for full Prescribing Information or visit www.ONFI.com)
Rx Only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

See full Prescribing Information for complete boxed warning.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

INDICATIONS AND USAGE – ONFI® (clobazam) CIV is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

CONTRAINDICATIONS – ONFI is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Hypersensitivity reactions have included serious dermatological reactions *[see Warnings and Precautions in full PI]*.

WARNINGS AND PRECAUTIONS – Risks from Concomitant Use with Opioids: Concomitant use of benzodiazepines, including ONFI, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe ONFI concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when ONFI is used with opioids *[see Drug Interactions in full PI]*.

Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants: Since ONFI has a central nervous system (CNS) depressant effect, patients or their caregivers should be cautioned against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Drug Interactions in full PI]*.

Somnolence or Sedation: ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation was reported at all effective doses and was dose-related. In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of ONFI is known.

Withdrawal Symptoms: Abrupt discontinuation of ONFI should be avoided. ONFI should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation. Withdrawal symptoms occurred following abrupt discontinuation of ONFI; the risk of withdrawal symptoms is greater with higher doses. As with all antiepileptic drugs, ONFI should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. Withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to patients who received excessive doses over an extended period of time, followed by an abrupt discontinuation. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic doses for several months *[see Dosage and Administration and Warnings and Precautions in full PI]*.

Serious Dermatological Reactions: Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with ONFI in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. ONFI should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered *[see Contraindications in full PI]*.

Physical and Psychological Dependence: Patients with a history of substance abuse should be under careful surveillance when receiving ONFI or other psychotropic agents because of the predisposition of such patients to habituation and dependence *[see Drug Abuse and Dependence in full PI]*.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including ONFI, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing ONFI or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions in full PI]*.

ADVERSE REACTIONS – Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. During its development for the adjunctive treatment of seizures associated with LGS, ONFI was administered to 333 healthy volunteers and 300 patients with a current or prior diagnosis of LGS, including 197 patients treated for 12 months or more. The conditions and duration of exposure varied greatly and included single- and multiple-dose clinical pharmacology studies in healthy volunteers and two double-blind studies in patients with LGS (Study 1 and 2) *[see Clinical Studies in full PI]*. Only Study 1 included a placebo group, allowing comparison of adverse reaction rates on ONFI at several doses to placebo. Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled Clinical Trial (Study 1): The adverse reactions associated with ONFI treatment discontinuation in ≥1% of patients in decreasing order of frequency included lethargy, somnolence, ataxia, aggression, fatigue, and insomnia. Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial (Study 1): Table 3 lists the adverse reactions that occurred in ≥5% of ONFI-treated patients (at any dose), and at a rate greater than placebo-treated patients, in the randomized, double-blind, placebo-controlled, parallel group clinical study of adjunctive AED therapy for 15 weeks (Study 1).

Table 3. Adverse Reactions Reported for ≥5% of Patients and More Frequently than Placebo in Any Treatment Group

		ONFI Dose Level			All ONFI N=179 %
	Placebo N=59 %	Low[a] N=58 %	Medium[b] N=62 %	High[c] N=59 %	
Gastrointestinal Disorders					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
General Disorders and Administration Site Conditions					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
Infections and Infestations					
Upper respiratory tract infection	10	10	13	14	12
Pneumonia	2	3	3	7	4
Urinary tract infection	0	2	5	5	4
Bronchitis	0	2	0	5	2
Metabolism and Nutrition Disorders					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
Nervous System Disorders					
Somnolence or Sedation	15	17	27	32	26
Somnolence	12	16	24	25	22
Sedation	3	2	3	9	5
Lethargy	5	10	5	15	10
Drooling	3	0	13	14	9
Ataxia	3	3	2	10	5
Psychomotor hyperactivity	3	3	3	5	4
Dysarthria	0	2	2	5	3
Psychiatric Disorders					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
Respiratory Disorders					
Cough	0	3	5	7	5

[a] Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight

[b] Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight

[c] Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

Post Marketing Experience: These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class. *Blood Disorders:* Anemia, eosinophilia, leukopenia, thrombocytopenia; *Eye Disorders:* Diplopia, vision blurred; *Gastrointestinal Disorders:* Abdominal distention; *General Disorders and Administration Site Conditions:* Hypothermia; *Investigations:* Hepatic enzyme increased; *Musculoskeletal:* Muscle spasms; *Psychiatric Disorders:* Agitation, anxiety, apathy, confusional state, depression, delirium, delusion, hallucination; *Renal and Urinary Disorders:* Urinary retention; *Respiratory Disorders:* Aspiration, respiratory depression; *Skin and Subcutaneous Tissue Disorders:* Rash, urticaria, angioedema, and facial and lip edema.

DRUG INTERACTIONS – Opioids: The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation *[see Warnings and Precautions in full PI]*.

CNS Depressants and Alcohol: Concomitant use of ONFI with other CNS depressants may increase the risk of sedation and somnolence. Alcohol, as a CNS depressant, will interact with ONFI in a similar way and also increases clobazam's maximum plasma exposure by approximately 50%. Therefore, caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol, and caution that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Warnings and Precautions in full PI]*.

Effect of ONFI on Other Drugs: Hormonal Contraceptives: ONFI is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with ONFI. Additional non-hormonal forms of contraception are recommended when using ONFI *[see Clinical Pharmacology and Patient Counseling Information in full PI]*. Drugs Metabolized by CYP2D6: ONFI inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary *[see Clinical Pharmacology in full PI]*.

Effect of Other Drugs on ONFI: Strong and moderate inhibitors of CYP2C19: Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam, the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions. Dosage adjustment of ONFI may be necessary when co-administered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) *[see Clinical Pharmacology in full PI]*.

USE IN SPECIFIC POPULATIONS – Pregnancy: Pregnancy Category C. Risk Summary: There are no adequate and well-controlled studies of ONFI in pregnant women. In animal studies, administration of clobazam during pregnancy resulted in developmental toxicity, including increased incidences of fetal malformations, at plasma exposures for clobazam and its major active metabolite, N-desmethylclobazam, below those expected at therapeutic doses in patients. ONFI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Available human data on the risk of teratogenicity associated with benzodiazepines are inconclusive. There is insufficient evidence in humans to assess the effect of benzodiazepine exposure during pregnancy on neurodevelopment. Administration of benzodiazepines immediately prior to or during childbirth can result in a syndrome of hypothermia, hypotonia, respiratory depression, and difficulty feeding. In addition, infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Data for other benzodiazepines suggest the possibility of adverse developmental effects (including long-term effects on neurobehavioral and immunological function) in animals following prenatal exposure to benzodiazepines at clinically relevant doses. Data: *Animal:* In a study in which clobazam (150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryofetal mortality and incidences of fetal skeletal variations were increased at all doses. The low-effect dose for embryofetal developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, lower than those in humans at the maximum recommended human dose (MRHD) of 40 mg/day. Oral administration of clobazam (10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality at the high dose. Incidences of fetal variations were increased at all doses. The highest dose tested was associated with maternal toxicity (ataxia and decreased activity). The low-effect dose for embryofetal developmental toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD. Oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryofetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behavior (locomotor activity) at all doses. The low-effect dose for adverse effects on pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD. Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to ONFI, physicians are advised to recommend that pregnant patients taking ONFI enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves or their caregiver. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Nursing Mothers: ONFI is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ONFI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in patients less than 2 years of age have not been established. In a study in which clobazam (4, 36, or 120 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 14 to 48), adverse effects on growth (decreased bone density and bone length) and behavior (altered motor activity and auditory startle response; learning deficit) were observed at the high dose. The effect on bone density, but not on behavior, was reversible when drug was discontinued. The no-effect level for juvenile toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to clobazam and its major active metabolite, N-desmethylclobazam, less than those expected at therapeutic doses in pediatric patients.

Geriatric Use: Clinical studies of ONFI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly subjects appear to eliminate clobazam more slowly than younger subjects based on population pharmacokinetic analysis. For these reasons, the initial dose in elderly patients should be 5 mg/day. Patients should be titrated initially to 10-20 mg/day. Patients may be titrated further to a maximum daily dose of 40 mg if tolerated *[see Dosage and Administration and Clinical Pharmacology in full PI]*.

CYP2C19 Poor Metabolizers: Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended *[see Dosage and Administration and Clinical Pharmacology in full PI]*.

Renal Impairment: The pharmacokinetics of ONFI were evaluated in patients with mild and moderate renal impairment. There were no significant differences in systemic exposure (AUC and C_{max}) between patients with mild or moderate renal impairment and healthy subjects. No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with ONFI in patients with severe renal impairment or ESRD. It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable *[see Dosage and Administration and Clinical Pharmacology in full PI]*.

Hepatic Impairment: ONFI is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of ONFI. For this reason, dosage adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment *[see Dosage and Administration and Clinical Pharmacology in full PI]*.

DRUG ABUSE AND DEPENDENCE – Controlled Substance: ONFI contains clobazam which is a Schedule IV controlled substance.

Abuse: ONFI can be abused in a similar manner as other benzodiazepines, such as diazepam. The pharmacological profile of ONFI is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on $GABA_A$ receptors, which leads to sedation and somnolence. The World Health Organization epidemiology database contains reports of drug abuse, misuse, and overdoses associated with clobazam *[see Drug Abuse and Dependence in full PI]*.

Dependence: Dependence: In clinical trials, cases of dependency were reported following abrupt discontinuation of ONFI. The risk of dependence is present even with use of ONFI at the recommended dose range over periods of only a few weeks. The risk of dependence increases with increasing dose and duration of treatment. The risk of dependence is increased in patients with a history of alcohol or drug abuse *[see Drug Abuse and Dependence in full PI]*. Withdrawal: Abrupt discontinuation of ONFI causes withdrawal symptoms. As with other benzodiazepines, ONFI should be withdrawn gradually. In ONFI clinical pharmacology trials in healthy volunteers, the most common withdrawal symptoms after abrupt discontinuation were headache, tremor, insomnia, anxiety, irritability, drug withdrawal syndrome, palpitations, and diarrhea. Other withdrawal reactions to clobazam reported in the literature include restlessness, panic attacks, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, blurred vision, photophobia, and muscle pain and stiffness. In general, benzodiazepine withdrawal may cause seizures, psychosis, and hallucinations *[see Dosage and Administration and Warnings and Precautions in full PI]*.

OVERDOSAGE – Signs and Symptoms of Overdosage: Overdose and intoxication with benzodiazepines, including ONFI, may lead to CNS depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension, and, rarely, coma or death. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including alcohol.

Management of Overdosage: The management of ONFI overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathomimetic agents. The efficacy of supplementary administration of physostigmine (a cholinergic agent) or of flumazenil (a benzodiazepine antagonist) in ONFI overdose has not been assessed. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions. Its use in patients with epilepsy is typically not recommended.

Lundbeck
Deerfield, IL 60015, U.S.A.

December 2016 CLB-L-00016c

RARE NEUROLOGICAL DISEASE SPECIAL REPORT

A SUPPLEMENT TO *NEUROLOGY REVIEWS*

In Primary Periodic Paralysis

Helping to turn limitation into activation

KEVEYIS® (dichlorphenamide) is the first and only FDA-approved treatment for hyperkalemic, hypokalemic, and related variants of Primary Periodic Paralysis (PPP).

KEVEYIS can help patients gain greater control over PPP by decreasing the number, severity, and duration of attacks[1,2]

- The efficacy of KEVEYIS has been proven in 2 clinical studies[1]
- KEVEYIS has a demonstrated safety profile[1]

Call 844-KEVEYIS (538-3947) for Patient Support

Learn more about PPP and KEVEYIS at ABOUTKEVEYIS.COM

Important Safety Information

Contraindications

Hypersensitivity to dichlorphenamide or other sulfonamides

Concomitant use of KEVEYIS and high-dose aspirin

Severe pulmonary disease, limiting compensation to metabolic acidosis caused by KEVEYIS

Hepatic insufficiency: KEVEYIS may aggravate hepatic encephalopathy

Warnings and Precautions

Hypersensitivity/Anaphylaxis/Idiosyncratic Reactions
Fatalities associated with the administration of sulfonamides have occurred due to adverse reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Pulmonary involvement can occur in isolation or as part of a systemic reaction.

Discontinue KEVEYIS at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction.

Concomitant Use of Aspirin
Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin. The concomitant use of KEVEYIS and high-dose aspirin is contraindicated. Use with caution in patients receiving low-dose aspirin.

Hypokalemia
KEVEYIS increases potassium excretion and can cause hypokalemia. The risk of hypokalemia is greater when KEVEYIS is used in patients with conditions associated with hypokalemia (eg, adrenocortical insufficiency, hyperchloremic metabolic acidosis, or respiratory acidosis), and in patients receiving other drugs that may cause hypokalemia (eg, loop diuretics, thiazide diuretics, laxatives, antifungals, penicillin, and theophylline).

Baseline and periodic measurements of serum potassium are recommended.

If hypokalemia develops or persists, consider reducing the dose or discontinuing KEVEYIS.

Metabolic Acidosis
KEVEYIS can cause hyperchloremic non–anion gap metabolic acidosis.Concomitant use of KEVEYIS with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis.

Baseline and periodic measurements of serum bicarbonate are recommended.

If metabolic acidosis develops or persists, consider reducing the dose or discontinuing KEVEYIS.

Falls
KEVEYIS increases the risk of falls; risk is greater in the elderly and with higher doses. Consider dose reduction or discontinuation of KEVEYIS in patients who experience falls while treated with KEVEYIS.

Pregnancy and Lactation

Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known in humans whether dichlorphenamide is excreted in human milk; exercise caution when administered to a nursing woman.

Adverse Reactions

The most common adverse reactions seen in clinical trials (incidence ≥ 10% and greater than placebo) include paresthesias, cognitive disorder, dysgeusia, and confusional state.

Please see Brief Summary of Prescribing Information on the next page.

KEVEYIS®
dichlorphenamide 50 mg tablets

GREATER CONTROL. LESS LIMITATION.

STRONGBRIDGE BIOPHARMA

References: 1. KEVEYIS Prescribing Information. Feasterville-Trevose, PA: Strongbridge Biopharma; 2017.
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KEV-0132 08/2017

KEVEYIS®
dichlorphenamide 50 mg tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEVEYIS® safely and effectively. See Full Prescribing Information for KEVEYIS®.

INDICATIONS AND USAGE

KEVEYIS is indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

DOSAGE AND ADMINISTRATION

Initiate dosing at 50 mg twice daily. The initial dose may be increased or decreased based on individual response, at weekly intervals (or sooner in case of adverse reaction). The maximum recommended total daily dose is 200 mg.

Primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants are a heterogeneous group of conditions, for which the response to KEVEYIS may vary. Therefore, prescribers should evaluate the patient's response to KEVEYIS after 2 months of treatment to decide whether KEVEYIS should be continued.

CONTRAINDICATIONS

KEVEYIS is contraindicated in the following circumstances:

- Hypersensitivity to dichlorphenamide or other sulfonamides
- Concomitant use of KEVEYIS and high dose aspirin
- Severe pulmonary disease, limiting compensation to metabolic acidosis caused by KEVEYIS
- Hepatic insufficiency: KEVEYIS may aggravate hepatic encephalopathy.

WARNINGS AND PRECAUTIONS

Hypersensitivity / Anaphylaxis / Idiosyncratic Reactions

Fatalities associated with the administration of sulfonamides have occurred due to adverse reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Pulmonary involvement can occur in isolation or as part of a systemic reaction.

KEVEYIS should be discontinued at the first appearance of skin rash or any sign of immune-mediated or idiosyncratic adverse reaction.

Concomitant Use of Aspirin

Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin. The concomitant use of KEVEYIS and high dose aspirin is contraindicated. KEVEYIS should be used with caution in patients receiving low dose aspirin.

Hypokalemia

KEVEYIS increases potassium excretion and can cause hypokalemia.

The risk of hypokalemia is greater when KEVEYIS is used in patients with conditions associated with hypokalemia (e.g., adrenocortical insufficiency, hyperchloremic metabolic acidosis, or respiratory acidosis), and in patients receiving other drugs that may cause hypokalemia (e.g., loop diuretics, thiazide diuretics, laxatives, antifungals, penicillin, and theophylline).

Baseline and periodic measurement of serum potassium during KEVEYIS treatment are recommended.

If hypokalemia develops or persists, consideration should be given to reducing the dose or discontinuing KEVEYIS.

Metabolic Acidosis

KEVEYIS can cause hyperchloremic non-anion gap metabolic acidosis. Concomitant use of KEVEYIS with other drugs that cause metabolic acidosis may increase the severity of metabolic acidosis.

Baseline and periodic measurement of serum bicarbonate during KEVEYIS treatment are recommended.

If metabolic acidosis develops or persists, consideration should be given to reducing the dose or discontinuing KEVEYIS.

Falls

KEVEYIS increases the risk of falls. The risk of falls is greater in the elderly and with higher doses of KEVEYIS. Consider dose reduction or discontinuation of KEVEYIS in patients who experience falls while treated with KEVEYIS.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 9-week randomized controlled trial in adults with hyperkalemic or hypokalemic periodic paralysis (Study 1), the most common adverse reactions in patients treated with KEVEYIS, with rates greater than placebo, were paresthesia, cognitive disorder, dysgeusia, and confusional state. The mean dose of KEVEYIS was 94 mg/day in patients with hypokalemic periodic paralysis and 82 mg/day in patients with hyperkalemic periodic paralysis.

Adverse Reactions in Patients Treated with KEVEYIS with Incidence ≥ 5% and more common than in Patients Treated with Placebo in Study 1

	Adverse Reaction	KEVEYIS N = 36 (%)	Placebo N = 29 (%)
Nervous system disorders	Paresthesia	44	14
	Cognitive disorder*	14	7
	Dysgeusia	14	0
	Confusional state	11	0
	Headache	8	7
	Hypoesthesia	8	0
	Lethargy	8	0
	Dizziness	6	0
Gastrointestinal disorders	Diarrhea	6	3
	Nausea	6	0
General disorders and administration site conditions	Fatigue	8	0
	Malaise	6	0
Investigations	Weight decreased	6	0
Musculoskeletal and connective tissue disorders	Muscle spasms	8	0
	Arthralgia	6	3
	Muscle twitching	6	0
Respiratory	Dyspnea	6	0
	Pharyngolaryngeal pain	6	0
Skin	Rash	8	0
	Pruritus	6	0

* Cognitive disorder combined cases with the preferred terms of cognitive disorder, disturbance in attention, and mental impairment.

The following are adverse reactions which have been reported for dichlorphenamide that were serious adverse events or are not reported in the previous section of labeling: amnesia, cardiac failure, condition aggravated, convulsion, fetal death, hallucination, nephrolithiasis, pancytopenia, psychotic disorder, renal tubular necrosis, stupor, syncope, and tremor.

DRUG INTERACTIONS

Aspirin and Salicylates

KEVEYIS may cause an elevation in salicylate levels in patients receiving aspirin. Anorexia, tachypnea, lethargy, and coma have been reported with concomitant use of dichlorphenamide and high-dose aspirin.

Concomitant use of KEVEYIS and high dose aspirin is contraindicated. KEVEYIS should be used with caution in patients receiving low dose aspirin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Teratogenic effects (fetal limb reduction defects) were reported following oral administration of dichlorphenamide to pregnant rats during organogenesis at 350 mg/kg, or 17 times the maximum recommended human dose (200 mg/day) on a body surface area (mg/m^2) basis. A no-effect dose has not been established. KEVEYIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether dichlorphenamide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dichlorphenamide is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

The risk of falls and of metabolic acidosis are greater in elderly patients.

OVERDOSAGE

Symptoms of overdosage or toxicity may include drowsiness, anorexia, nausea, vomiting, dizziness, paresthesias, ataxia, tremor, and tinnitus.

In the event of overdosage, induce emesis or perform gastric lavage. The electrolyte disturbance most likely to be encountered from overdosage is hyperchloremic acidosis.

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STRONGBRIDGE BIOPHARMA

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EDITOR'S NOTE

Glenn S. Williams

In 2018, *Neurology Reviews* celebrates its 25th anniversary and our *Rare Neurological Disease Special Report* turns four. I'm proud to say that this fourth annual issue is bigger and better than ever. We have a stellar lineup of authors, including Bernard Maria, MD; Ann Tilton, MD; Patricia McGoldrick, NP, MPA, MSN, and Steven Wolfe, MD; Jesus Eric Piña-Garza, MD; Gerald Salen, MD; Lianna Orlando, PhD, and Grace Pavlath, PhD; Ronald DeBellis, PharmD, and Micaila Ruiz, PharmD, RPh; Karen Orjuela, MD; Paul Melmeyer; and William Pardridge, MD. We also feature valuable contributions from Keck Graduate Institute students Russle Benson, Jae Chang, Vivek Banapur, Ilona Kravtsova, Jennifer Nguyen, and Caroline Kim.
A special thanks goes to Ron DeBellis, without whose assistance this issue would not have been possible. Thanks also to Elizabeth Katz, the publisher. I am indebted to her for her tireless work and constant support.

—Glenn S. Williams | Vice President, Group Editor | *Neurology Reviews*

A NOTE FROM NORD

Peter L. Saltonstall

As we celebrate the 35th anniversary of NORD and the *Orphan Drug Act,* we would be remiss if we did not acknowledge the incredibly important role that you, as a medical professional, play in your patients' lives.

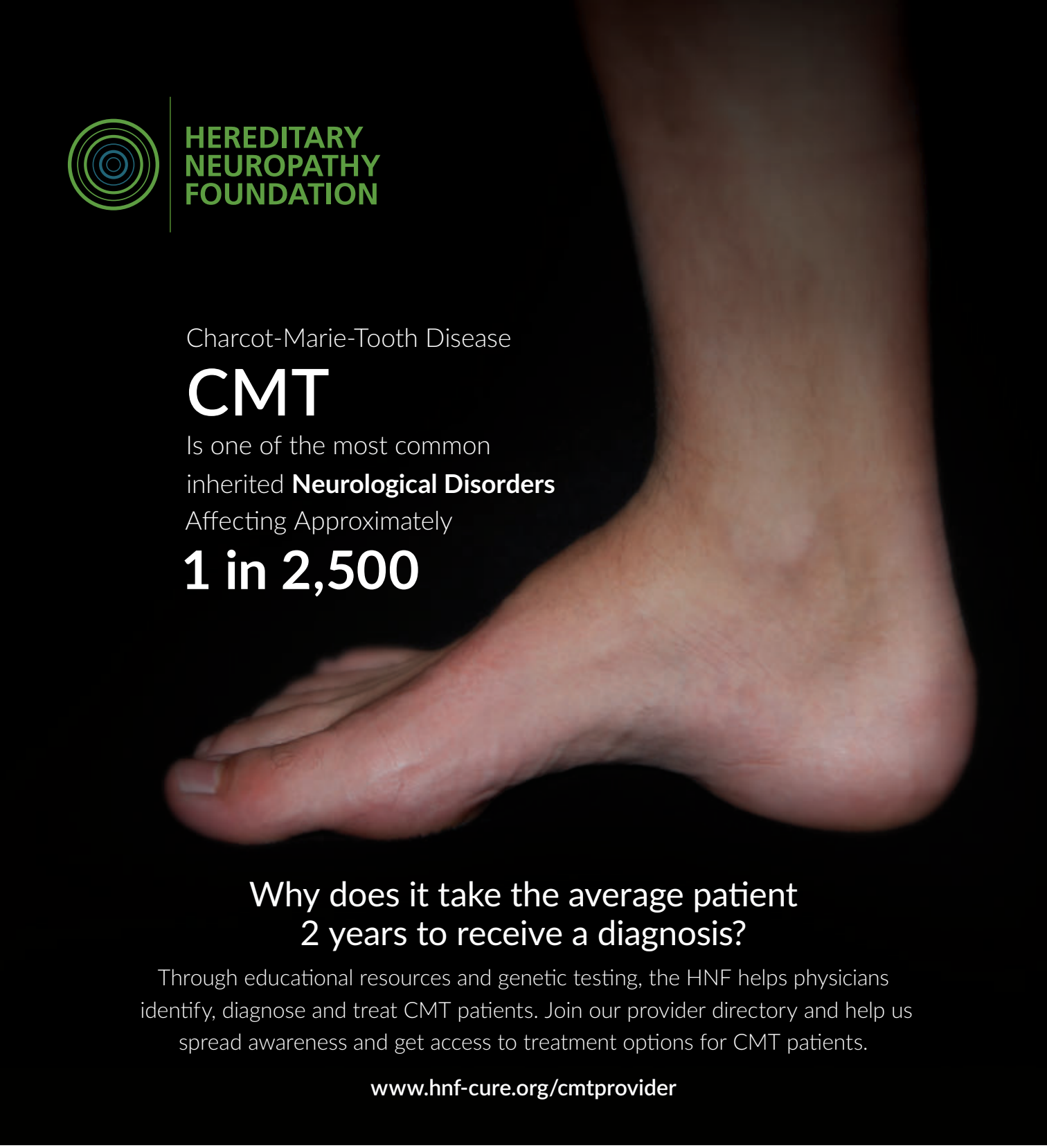
Patients and caregivers affected by rare medical conditions are particularly in need of, and grateful for, the support of their physicians and medical care teams. There are 7,000 diseases considered rare in the US and they are often lifelong, with a significant impact on the quality of life of those affected. About 85% of rare disorders have a genetic component.

Since 1983, NORD has been providing advocacy, education, patient/family services, and research on behalf of the 30 million Americans affected by rare diseases. On Capitol Hill, in university and medical school classrooms, at federal agencies including NIH and FDA, and in a host of other settings, NORD and our 270 member organizations promote awareness and advocate for research funding and public policies to assure patient access to diagnostic testing and treatment.

In this special anniversary issue, we are pleased to extend our gratitude to *Neurology Reviews* for their ongoing support for our educational outreach. We are also grateful to readers of this publication for your dedication to patients and your desire to access the most current information about rare diseases and related scientific advances.

We invite you to visit the NORD website frequently for information on specific rare diseases and to follow the latest rare disease news. To receive our monthly eNews and other news of interest to medical professionals, write to education@rarediseases.org.

—Peter L. Saltonstall | President and CEO | NORD



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Annual Patient-Centered Summit

Utilizes Voice Activation Technology to Capture Pain in Patient Reported Outcomes in CMT/HNPP

Allison Moore – *Founder & CEO/Principal Investigator*, Hereditary Neuropathy Foundation

On November 3, 2017, nearly 100 participants gathered at the Samberg Conference Center on the Massachusetts Institute of Technology (MIT) campus in Cambridge, MA for the Hereditary Neuropathy Foundation (HNF) Patient-Centered Charcot-Marie-Tooth (CMT) / Hereditary Neuropathy Pressure Palsies (HNPP) Pain Summit. The meeting brought together people with hereditary neuropathies and their family members, caregivers, clinicians, researchers, funding agencies, payors, leading pain experts and pharma industry to provide an in-depth look at chronic pain within the CMT/HNPP community, including its impact on quality of life. Funded in part by a Eugene Washington PCORI Engagement Award and industry partners; Pharnext Pharma, Acceleron Pharma, Flex Pharma and a grant from Pfizer, this one day conference offered expert sessions as well as breakout sessions, primarily patient-led, with a focus on patient engagement methods: all with an emphasis on identifying gaps that are hindering patient care in neuropathic and musculoskeletal pain, diagnosis and identifying biomarkers and outcome measures to support therapy development.

The prevalence of pain in this patient community became apparent during HNF's 2016 inaugural Patient-Centered CMT Summit. To validate this issue, HNF analyzed data from its Global Registry for Inherited Neuropathies (GRIN), to determine which co-morbidities were most prevalent and most important to patients. One question asked the one word they would use to describe their disease: ***pain*** was the number one response. As a result, HNF decided that the 2017 Summit needed to focus on assessing and addressing the gaps in pain management for the hereditary neuropathy patient community.

To further our knowledge of the patients experience on the impact pain is having on quality of life, and to inform the stakeholder community at the Summit, we captured the CMT patient's experience with pain in their own words. HNF partnered with the innovative, voice-powered survey platform, True Reply - www.truereply.com - to record patient responses to a 5-question survey in their own voice. The study was run over a 30-day period prior to the Summit. A total of 621 responses were recorded by 115 participants from the following questions:

The depth and variety of the patient responses to these questions were revelatory, but not surprising, to HNF Founder and CEO, Allison Moore:

"Hearing about our patients' experience with pain in their own words was both enlightening and heartbreaking at the same time. Our patients are hurting badly in so many ways, and they need guidance and protocols from their healthcare providers to help manage their pain so they can go about their daily lives as pain-free as possible."

KEY TAKEAWAYS FROM THE STUDY INCLUDED:

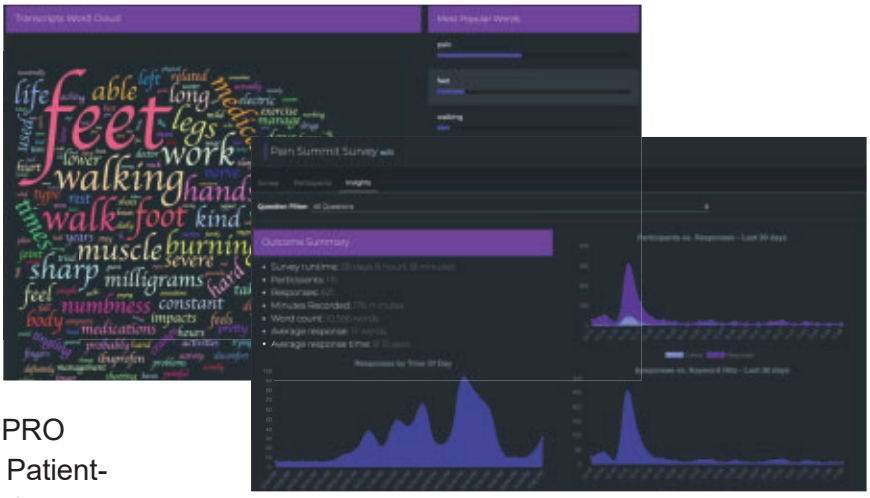
90% of patients indicated that their pain has a **moderate to severe impact** on their quality of life.

76% of patients are **managing their pain on their own**, with a combination of over-the-counter medications and alternative therapies.

63% of patients described their pain as **numbness, sharp, burning or stabbing**.

Jose Cotto, Founder and CEO of True Reply, helped HNF analyze and quantify the results. Said Jose:

"The ability of True Reply to quantitatively analyze patient responses in real-time while also giving researchers and clinicians access to qualitative data such patient voice tone, cadence and stress levels is a real game changer for Patient Reported Outcome (PRO) studies."



HNF is looking forward to integrating True Reply technology into future CMT PRO studies leading up to HNF's 3rd Annual Patient-Centered CMT Summit - www.cmtsummit.org - on September 29, 2018.

In addition, as part of the FDA's externally-led Patient-Focused Drug Development (PFDD) initiative, HNF will be hosting a PFDD meeting in Washington, D.C. on September 28th, the day before the Summit. FDA's PFDD initiative aims to more systematically obtain the patient's perspective on the burden of specific diseases and current treatments. This meeting will inform the FDA, drug developers and other key stakeholders, what is most important to patients and how patients view the benefits and risks of treatments for CMT.

"The voice of the CMT patient can no longer be ignored when it comes to the protocols, treatments and therapeutics that are being developed to treat this disease," says Allison. "We are looking forward to using technologies like True Reply to help us tell our patients' stories in their own words so we can address their immediate quality of life issues while waiting for desperately needed therapeutics to move through the pipeline and be approved for commercial use."

Hereditary Neuropathy Foundation

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The Widening Success of the 'Neurobiology of Disease in Children' Symposia

The impact of NDC symposia can be measured in attendance, publications, collaborations, research funding, and defining a path to discovery with research priorities.

Bernard L. Maria, MD

Since the days of Sir William Osler, medical societies in America have traditionally been organized by discipline or field of medicine, so that regular meetings of neuroscientists are with other neuroscientists (e.g., Society for Neuroscience), neurologists with other neurologists (American Academy of Neurology), and, for nearly 50 years, child neurologists with other child neurologists (Child Neurology Society [CNS]). However, advances in molecular biology, genetics, neuroimaging, neuropathology, and other key disciplines over the past 30 years have had great impact on understanding of basic mechanisms of neurological disease and unmasking opportunities for targeted interventions. To bring child neurologists who are seeing children with rare neurological conditions up to speed, therefore, requires engagement and participation of multiple scientific and clinical disciplines not routinely represented at annual CNS meetings.

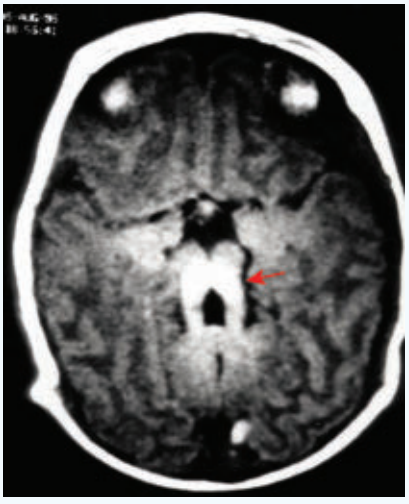
Origins of the Neurobiology of Disease in Children Symposium

In 1998, three years after discovering the molar tooth sign (see Figure) as the pathognomonic radiologic sign in Joubert syndrome and related disorders,[1,2] a group of rare neurogenetic conditions with hindbrain malformation presenting with neonatal hypotonia, apnea, and hyperpnea, as well as ocular motor apraxia and developmental delay, I obtained funding from the National Institute of Neurological Disorders and Stroke (NINDS) to hold an all-day satellite symposium on Joubert syndrome at the CNS Annual Meeting in Montreal, Quebec, Canada.

The first Neurobiology of Disease in Children (NDC) symposium was well attended by CNS members and extremely well received, despite considerable advance skepticism about members' interest in such a rare disease. Among the faculty were speakers and panelists from multiple disciplines, including radiology, psychology, developmental pediatrics, neuro-ophthalmology, genetics, neuropathology, and others who were not members of the Society or had ever attended a CNS Annual Meeting.

The proceedings of the symposium generated a consensus statement on the clinical features of Joubert syndrome,

FIGURE: Molar tooth sign



Thickened superior cerebellar peduncles (arrow), deep interpeduncular fossa, and hypoplastic superior cerebellar vermis can be seen.

Dr. Maria is in pediatric neurology practice in Morristown, New Jersey.

diagnostic criteria, and future research directions.[3] Because Marie Joubert, MD, had reported the first affected family in Montreal in 1969 (her achievement was later recognized when Prof. Dr. Eugen Boltshauser named the condition after her), we had a unique follow-up opportunity, with help from Frederick Andermann, MD, of the Montreal Neurological Institute, to re-examine (at the conference) a 31 year-old patient who was 11 months of age when the original proband was first reported by Dr. Joubert from the Montreal Children's Hospital (MCH). (To underscore the rarity of the condition, I had not heard of it until 1984, despite having completed pediatrics training at MCH, and then having left Montreal, in 1983.)

Examination of this patient disclosed intellectual disability as well as ocular motor apraxia, and, for the first time, lingual apraxia. The full proceedings of the first NDC symposium on Joubert syndrome were published in a stand-alone issue of the *Journal of Child Neurology* the following year.

Soon after the inaugural NDC meeting, my first mentor, Bernard Lemieux, MD, from the University of Sherbrooke in Quebec, suggested to me that a standing satellite meeting on rare diseases would be a welcome addition to CNS Annual Meetings. He encouraged me to seek additional funding from the National Institutes of Health. With encouragement from the CNS and lay foundations interested in highlighting rare diseases to the largest gathering of child neurologists, in 2001, NINDS funded the first five-year NDC conference grant (2001 through 2005); NDC has now successfully renewed NIH funding through four grant cycles (2001–2020; grant 5R13NS040925-20A1).

Impact of NDC on the Understanding of Rare Diseases

It is estimated that there are more than 7,000 rare diseases (defined by the NIH in part as conditions affecting fewer than 200,000 people) and that half—roughly 3,500—affect the developing nervous system of children. It is further estimated that 30% of children with a rare disease will not live to see their fifth birthday.[4,5] Many conditions produce profound dysfunction, and the toll on their family and their community more broadly is incalculable.

For this reason, NDC has had a wide range of important topics selected by its scientific advisory committee (see Table) to:

- review scientific and clinical advances
- determine the relevance of those advances to current and future clinical practice

TABLE. Topics at NDC symposia

Year	Topic
2001	Neurofibromatosis
2002	Leukodystrophy
2003	Tuberous sclerosis complex
2004	Rett syndrome
2005	Tourette syndrome
2006	Spinal muscular atrophy
2007	Central nervous system tumors
2008	Injury to the preterm brain and cerebral palsy
2009	Muscular dystrophy
2010	Cerebrovascular disease
2011	Childhood ataxia
2012	Batten disease
2013	Mitochondrial diseases
2014	Autism spectrum disorder
2015	Epileptic encephalopathy
2016	Neurofibromatosis
2017	Leukodystrophy
2018	Tourette syndrome
2019	CNS tumors
2020	Traumatic brain injury

Continued on page 14

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The Widening Success of the 'Neurobiology of Disease in Children' Symposia

Continued from page 12

- coordinate efforts among child neurologists (as well as across multiple clinical disciplines, research scientists, lay organizations, and the NIH)
- review current research initiatives
- highlight areas of clinical focus
- define future directions
- disseminate symposium proceedings, so that clinicians and scientists are informed about the latest scientific and clinical advances, current initiatives, and future directions in the field of child neurology and, more broadly, pediatric neuroscience.

Topics were selected on the basis of scientific advances, relevance to child neurology practice, lay foundation/association maturity, and the need to define future research priorities.

There are many examples of how understanding the basic mechanisms of a rare disease has produced breathtaking and life-transforming therapies. For example:

- Improved understanding of survival motor neuron 1 and 2 genes (SMN1 and SMN2) and the SMN complex that were discussed at the 2006 NDC conference on spinal muscular atrophy type 1 (Werdnig-Hoffman disease, a universally lethal disease until then[6]) opened the door to the first effective treatment with nusinersen, a SMN2-directed antisense oligonucleotide.
- Other advances in drugs that target pathogenic pathways in the tuberous sclerosis complex envisioned back in 2003 have since been developed[7] and substantially reduced tumor and epileptic burden.
- In neurofibromatosis, (the 2001 NDC conference, and again in 2016), we learned that, in the intervening years of the two meetings, there were more than 50 investigational drug studies in 2016, in contrast to *none* in 2001.
- In 2017, the second NDC symposium on leukodystrophy highlighted the fact that, since the first NDC symposium on leukodystrophy in 2002, there had been many important developments, including establishing several consortia, more than 1,500 PubMed citations, more than 40 new leukodystrophies described, improved understanding of the genetics and pathogenesis for the development of novel therapies, successful ex vivo gene therapy for adrenoleukodystrophy (ALD) and metachromatic leukodystrophy, and implementation of newborn screening for ALD and Krabbe disease.

It is fair to say that NDC has not only been a witness to amazing advances but that the gathering of experts has catalyzed discovery through consensus building on research priorities and mentored more than 250 young investigators.

Impact on the Child Neurology Community, Patients, and Families

It has been my privilege for the past 20 years to bring to the child neurology community the most highly respected experts on rare disorders that are of prime importance to this medical community. The impact of such an effort can be measured in attendance, publications, collaborations, research funding, and defining a path to discovery with research priorities. The attention given to NDC by the child neurology community has elevated rare disease to a central and standing part of the CNS's annual focus (on Day 1 of the Annual Meeting) for the past two decades.

The real impact on children and families of building awareness and equipping clinicians with the knowledge, skills, values and attitudes needed when they return to their practicing communities is harder to measure. My greatest satisfaction is knowing that this annual effort has developed young investigators (and not-so-young ones) to continue to move the field forward to lessen the burden of neurological disease on children and to help them lead lives that are as close to normal as possible.

All I ask is that my epitaph read "Exceptional wedding planner."

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Family Support & Empowerment Program
Child Neurology Foundation

A new service for your patients and their families from the Child Neurology Foundation

The Child Neurology Foundation (CNF) Family Support and Empowerment Program (FSEP) offers families a free, direct connection with an experienced, compassionate Peer Support Specialist to help navigate the journey of disease diagnosis, treatment, and management for a child living with neurologic condition.

How Can CNF's Peer Support Specialists Help Your Patients?
As a health care provider, you can provide comprehensive, family-centered care for your patients and families. Think of FSEP as a partner in achieving family-centered care and as a trusted resource.

FSEP's Peer Support Specialists can help answer the emotional or lifestyle questions your families may have related to their child's neurologic diagnosis such as:

- Does anyone know what I'm going through?
- How do I manage when there seems to be no answers or no good answers?
- How do I balance the needs of my other children?
- How do I explain this to family & friends?
- Now what?

Peer Support Specialists offer support born from their own life experiences and have received comprehensive training about the needs of the child neurology community. Since early 2017, FSEP has reached* families from 43 states and 40 countries, let us help your patients, too.

Please consider offering FSEP support services to your patients & families.
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www.childneurologyfoundation.org/FSEP

* as of January 2018

CHILD NEUROLOGY FOUNDATION'S SPECIAL SECTION

CNF is committed to serving as a collaborative center of education and support for children and families living with neurologic conditions. Learn more at www.childneurologyfoundation.org

Pediatric Spasticity

Ann Tilton, MD*, Professor of Neurology and Pediatrics, Department of Pediatric Neurology at Louisiana State University, President, Child Neurology Foundation, Vice President, American Academy of Neurology

Spasticity is a common feature of many chronic motor disorders affecting infants, children, and adolescents; defined as an exaggerated response to passive movement of a limb in which there is velocity dependent resistance of a muscle to stretch. Spasticity is characterized by:

- excessive and inappropriately timed activation of skeletal muscles, which may interfere with a child's ability to move voluntarily in a normal fashion;
- also affecting passive movement and posture; and
- must be differentiated from other manifestations of impaired movement, especially dystonia and rigidity, since treatment decisions are based upon the type of abnormal tone.

In the pediatric population spasticity is most commonly found in children with cerebral palsy. However, spasticity can result from damage or abnormal development of nerve cells or pathways controlling motor movement either in the brain or spinal cord. Thus, spasticity is not uncommonly seen in children with traumatic and hypoxic injury to the brain, stroke, spinal cord injury, and brain tumors. Spasticity may interfere with a child's control of voluntary movement, coordination, exercise tolerance and range of motion in the joints. As a result, spasticity can limit activities of daily living and may cause pain and disturbed sleep. In more severely affected individuals, patient care is often more difficult. Over time spasticity is associated with impaired muscle growth. If untreated there may be permanent shortening of muscles (contractures) and the development of bone and joint deformities. Therefore, proactive treatment of pediatric spasticity is suggested to maximize a child's quality of life.

Evaluation and goals of spasticity management

Evaluation of a child with spasticity includes a thorough neurologic examination to document the pattern and severity of spastic involvement and to determine how the muscle hypertonia is interfering with function and/or patient care. The exam should include:

- standardized measures of tone;
- assessment of motor performance;
- functional ability, and
- gait analysis may be helpful

The goal of treating muscle overactivity is to improve some aspect of care, comfort, or active function, and to prevent future musculoskeletal complications such as contractures and hip subluxation. Thus, treatment should include a team approach including the physicians and therapists as well a school and family to develop a complete picture of the child in the home and school environment. The family and patient are critical members of the team and together with the other team members develops a treatment plan that considers current abilities and disabilities, child and family goals, limitations such as finances and transportation, and other factors. Within the overall treatment plan, reduction of muscle overactivity will likely become an important strategy but should never be an end in itself.

There are several options available for the palliative treatment of pediatric spasticity, including:

- Intramuscular therapy
- Intrathecal therapy
- Rehabilitation therapy
- Selective dorsal rhizotomy
- Orthopedic surgery

In deciding on which treatment is optimal for an individual patient, consideration is given to whether the abnormal tone is focal (limited muscle groups) or generalized (multiple muscle groups) in involvement. If focal, then medications such as botulinum toxin or less often phenol are employed. When primary, the lower extremity is the therapeutic target in a strong young patient with the near ability to ambulate then selective dorsal rhizotomy is a consideration. If the generalized tone is the main issue, oral medications and intrathecal baclofen top the therapeutics considerations. Orthopedic intervention is also important for bony and joint deformities, contractures, and general management. Of course, many other factors are important in the decision making.

Conclusion

Treatment of spasticity remains a major therapeutic challenge in children with chronic motor disorders. Families

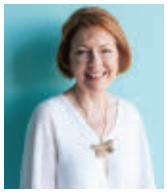
*Dr. Tilton is a consultant for Ipsen Pharmaceuticals. The Child Neurology Special Section is generally supported per a charitable sponsorship provided by Ipsen Pharmaceuticals.

often have a great deal of uncertainty about what treatment approach may be best for their child. In many ways the well–trained pediatric neurologist is an ideal physician to assist the family in making appropriate decisions regarding which spasticity intervention is most likely to produce benefit for their child and be in concert with their families' goals of care.

For more information, please visit:

www.ninds.nih.gov/Disorders/All-Disorders/Spasticity-Information-Page

www.childneurologyfoundation.org/disorders/cerebral-palsy/



A Child's Dream. A Mother's Love.

Debbie Fragner
Founder & Executive Director, Children's Cerebral Palsy Movement

Cerebral palsy (CP) doesn't discriminate. It impacts every demographic in America; one out of every 323 live births. I should know because my daughter, Maddie, was one of those children. Born three months premature with a bilateral brain bleed requiring a complex hospital stay, her infantile CP diagnosis upended our family's lives. Recognizing my purpose, I left corporate America to care for our little girl.

Mahatma Gandhi once said, "Be the change you wish to see in the world." I took this advice to heart, advocating for Maddie to receive the fullest possible life. Knowing that the best way to teach others how to treat you is by showing them how to act, we showed others how to treat our child. From day one, we never allowed limits to be placed on her, not even by doctors. We resolved to stay hopeful, allowing for positive outcomes. Never once did we, in fact, even mention the diagnosis to Maddie until she turned eight.

Our physical actions matched our mental vigilance. We pursued intensive early intervention, including physical therapy and occupational therapy. Resolved to do whatever it took, we carved our own holistic medical path, blending integrative medicine with nutrition to mitigate mitochondrial strain. To stave off spasticity, we employed unconventional but promising therapeutic approaches, including, therapeutic horseback riding, neurologic music therapy, hyperbaric oxygen therapy, intramuscular therapy, acupuncture, therapeutic swimming, and more.

For years on end, Maddie dutifully gave her all in up to 10 therapy sessions per week, all while trying to succeed as a mainstreamed student. Finally, she was the one to teach me how to treat her—she told me she wanted a more normal life.

Though our orthopedist was initially unsure of our use of holistic treatments combined with conventional methods, even he has since changed his mind, acknowledging that our unparalleled research and thoughtful decision making that went in to each decision was something to respect. The subsequent successes spoke for themselves and compelled him to reconsider how he cares for his CP patients. Largely, I can say our combined hard efforts paid off. In fact, no fewer than two doctors have called my daughter a miracle child. They didn't have to tell us this, though. We instinctively knew all along that CP is a diagnosis, not a destiny.

Children's Cerebral Palsy Movement: Engaging With Engaging Treatment

Children's Cerebral Palsy Movement
A DIAGNOSIS, NOT A DESTINY

After more than eight years of enduring countless hours of therapy, Maddie told me she wanted a life in spite of cerebral palsy. She wanted to dance ballet!

My quest to help her revealed a critical gap in the realm of CP rehabilitation. Due to lack of government funding, precious opportunities remained untapped. Eureka! I had a vision: why not use highly motivating 'exercise as medicine'? Help CP children engage in a physical activity they would love, while achieving therapeutic benefit. The result? A nonprofit, Children's Cerebral Palsy Movement, poised to transform the American CP landscape.

Our nonprofit designed, funded, and tested an innovative therapeutic dance program, Ability Ballet, rendering statistically significant improvements in cognition, physical function and feelings of self-worth in participating children with CP. Building on our success, we expanded our vision by developing much needed community programs for children with CP and their families living in isolation, often without hope.

With a focus on uniting and providing support, our plan is to address daily needs while improving quality of life and long-term outcomes. Through our efforts, we have thrived in designing meaningful programs, including our first annual Cerebral Palsy Kids Walk/Run on March 3rd; a CP Family Forum in collaboration with UCLA Orthopedic Institute on March 17; professionally facilitated support groups and educational seminars designed for CP caregivers; academic tutoring to bridge learning gaps for mind-capable fully mainstreamed CP children; Ability Ballet classes; and a host of social and fun activities for deserving CP children and families.

I am thankful for the bravery of Maddie and other kids like her; they remind me that by working together, nothing is impossible.

To learn more about CCPM, visit: www. childrens cerebralpalsymovement.org

The **FIRST** and **ONLY FDA-APPROVED** botulinum toxin for the treatment of **LOWER LIMB SPASTICITY** in pediatric patients 2 years of age and older[1]

Loosen the hold of lower limb spasticity

for 4 to 5½ months* in most patients[1]

*The majority of patients in the clinical study were retreated between 16 and 22 weeks; however, some patients had a longer duration of response. The degree and pattern of muscle spasticity and overall clinical benefit at the time of re-injection may necessitate alterations in the dose of Dysport® and the muscles to be injected. Re-treatment, based on return of clinical symptoms, should not occur in intervals of less than 12 weeks.[1]

INDICATIONS

Dysport® (abobotulinumtoxinA) for injection is indicated for the treatment of:

- Adults with cervical dystonia
- Spasticity in adult patients
- Lower limb spasticity in pediatric patients 2 years of age and older

IMPORTANT SAFETY INFORMATION

Warning: Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of Dysport and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on following pages.

Dysport® provided significant results in both treatment groups vs placebo across co-primary efficacy endpoints[1,2]

- A multicenter, prospective, double-blind, randomized, placebo-controlled study assessing Dysport® (abobotulinumtoxinA) in patients 2 to 17 years of age with lower limb spasticity because of cerebral palsy causing dynamic equinus foot deformity
- Significant improvement in ankle plantar flexor muscle tone as determined by mean change in **Modified Ashworth Scale (MAS)** at Week 4 (primary endpoint) and Week 12 ($P<0.05$)
- Significant improvement in response to treatment as determined by mean **Physician's Global Assessment (PGA)** at Week 4 (primary endpoint) and Week 12 ($P<0.05$)

Safety assessed in 160 Dysport® treated pediatric patients[1]

- The most commonly observed adverse reactions (≥10% of patients in any group and greater than placebo) were upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough, and pyrexia

Dysport® offers a full complement of support services

Faculty bureau-led live training

- Healthcare professionals sign up for Dysport® injection training by visiting www.Dysport.com

IPSEN CARES®

- Offers a single point of contact for patients and healthcare professionals to help with **benefits verification, copay assistance, and more**. **Visit www.IpsenCares.com to learn more**

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

Dysport is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components; or in the presence of infection at the proposed injection site(s); or in patients known to be allergic to cow's milk protein. Hypersensitivity reactions including anaphylaxis have been reported.

Dysport®
(abobotulinumtoxinA)

Time Between Treatments

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of Dysport are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products, and, therefore, units of biological activity of Dysport cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Dysphagia and Breathing Difficulties

Treatment with Dysport and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant side effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of Dysport.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of Dysport for the treatment of hyperhidrosis has not been established. Dysport is approved only for intramuscular injection.

Most Common Adverse Reactions

Adults with upper limb spasticity (≥2% and greater than placebo): nasopharyngitis, urinary tract infection, muscular weakness, musculoskeletal pain, dizziness, fall, and depression.

Adults with lower limb spasticity (≥ 5% and greater than placebo): falls, muscular weakness, and pain in extremity.

Adults with cervical dystonia (≥5% and greater than placebo): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain, and eye disorders.

Pediatric patients with lower limb spasticity (≥10% and greater than placebo): upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough, and pyrexia.

Drug Interactions

Co-administration of Dysport and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of Dysport may potentiate systemic anticholinergic effects, such as blurred vision. The effect of administering different botulinum neurotoxins at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of Dysport.

Use in Pregnancy

Based on animal data, Dysport may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Dysport should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediatric Use

Based on animal data, Dysport may cause atrophy of injected and adjacent muscles; decreased bone growth, length, and mineral content; delayed sexual maturation; and decreased fertility.

Geriatric Use

In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant disease and other drug therapy. Subjects aged 65 years and over who were treated with Dysport for lower limb spasticity reported a greater percentage of fall and asthenia as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact Ipsen at 1-855-463-5127. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: 1. Dysport® (abobotulinumtoxinA) [Prescribing Information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; June 2017. **2.** Data on file. Ipsen Biopharmaceuticals, Inc. Basking Ridge, NJ.

Dysport®
(abobotulinumtoxinA)
Time Between Treatments

Please see Brief Summary of Full Prescribing Information, including **Boxed Warning**, on following pages.

DYSPORT® (abobotulinumtoxinA) for injection, for intramuscular use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

BOXED WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of DYSPORT and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose.

INDICATIONS AND USAGE:

Dysport® (abobotulinumtoxinA) for injection is indicated for the treatment of:

- Spasticity in adult patients
- Adults with cervical dystonia
- Lower limb spasticity in pediatric patients 2 years of age and older.

CONTRAINDICATIONS: DYSPORT is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation; or infection at the proposed injection site(s). Hypersensitivity reactions have been reported, including anaphylaxis. This product may contain trace amounts of cow's milk protein. Patients known to be allergic to cow's milk protein should not be treated with DYSPORT.

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products: The potency Units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect: Post-marketing safety data from DYSPORT and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including upper limb spasticity in children and approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than the maximum recommended total dose.

Dysphagia and Breathing Difficulties: Treatment with DYSPORT and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Pre-existing Neuromuscular Disorders: Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT.

Human Albumin and Transmission of Viral Diseases: This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

Intradermal Immune Reaction: The possibility of an immune reaction when injected intradermally is unknown. The safety of DYSPORT for the treatment of hyperhidrosis has not been established. DYSPORT is approved only for intramuscular injection.

ADVERSE REACTIONS

Cervical Dystonia (CD): DYSPORT exposure data in 446 CD patients in 7 studies; two were randomized, double-blind, single treatment, placebo-controlled studies with subsequent optional open-label treatment in which dose optimization (250 to 1000 Units per treatment) over the course of 5 treatment cycles was allowed. Population: Caucasian (99%); median age 51 (range 18–82 years); (87%) less than 65 years of age; 58.4% women. In placebo-controlled trials the most common adverse reactions (>5%) reported in patients receiving DYSPORT 500 Units were muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain and eye disorders (consisting of blurred vision, diplopia, and reduced visual acuity and accommodation). Other than injection site reactions, most adverse reactions became noticeable about one week after treatment and lasted several weeks. The rates of adverse reactions were higher in the combined controlled and open-label experience than in the placebo-controlled trials. Two patients (<1%) experienced adverse reactions leading to withdrawal and one experienced disturbance in attention, eyelid disorder, feeling abnormal and headache, and one patient experienced dysphagia. Most commonly reported adverse reactions ≥5% and greater than placebo) in patients who received DYSPORT 500 Units (N=173) vs. placebo (N=182), respectively were: **Any Adverse Reaction** (61%, 51%); **General disorders and administration site conditions** (30%, 23%), Injection site discomfort (13%, 8%), Fatigue (12%, 10%), Injection site pain (5%, 4%); **Musculoskeletal and connective tissue disorders** (30%, 18%), Muscular weakness (16%, 4%), Musculoskeletal pain (7%, 3%), **Gastrointestinal disorders** (28%, 15%), Dysphagia (15%, 4%), Dry mouth (13%, 7%); **Nervous system disorders** (16%, 13%), Headache (11%, 9%); **Infections and infestations** (13%, 9%); **Respiratory, thoracic and mediastinal disorders** (12%, 8%), Dysphonia (6%, 2%); **Eye disorders** [vision blurred, diplopia, visual acuity, reduced, eye pain, eyelid disorder, accommodation disorder, dry eye, eye pruritus] (7%, 2%). In a randomized, multiple fixed-dose study, the common adverse reactions (dose divided between two muscles–sternocleidomastoid and splenius capitis) for patients who received Placebo or DYPORT dose of either 250 Units, 500 Units, 1000 Units, respectively were: **Any Adverse Event** (30%, 37%, 65%, 83%); Dysphagia (5%, 21%, 29%, 39%); Dry mouth (10%, 21%, 18%, 39%); Muscular weakness (0%, 11%, 12%, 56%); Injection site discomfort (10%, 5%, 18%, 22%); Dysphonia (0%, 0%, 18%, 28%); Facial paresis (0%, 5%, 0%, 11%); and Eye disorders [vision blurred, diplopia, visual acuity, reduced, eye pain, eyelid disorder, accommodation disorder, dry eye, eye pruritus] (0%, 0%, 6%, 17%).

Injection Site Reactions: Injection site discomfort and injection site pain were common adverse reactions following DYSPORT administration.

Less Common (<5%) Reported Adverse Reactions During Double-Blind Phase of Clinical Trials: *Breathing Difficulty* reported by ~ 3% DYSPORT patients vs 1% of placebo patients, consisted mainly of dyspnea. The median time to onset from last dose of DYSPORT was approximately one week; median duration was approximately three weeks. Other adverse reactions (<5%) in the DYSPORT 500 Units group vs. placebo, respectively included dizziness (3.5%, 1%), and muscle atrophy (1%, 0%).

Laboratory Findings: Patients treated with DYSPORT exhibited a small increase from baseline (0.23 mol/L) in mean blood glucose relative to placebo-treated patients. This was not clinically significant among patients in the development program but could be a factor in patients whose diabetes is difficult to control.

Electrocardiographic Findings: ECG measurements were only recorded in a limited number of patients in an open-label study without a placebo or active control. This study showed a statistically significant reduction in heart rate compared to baseline, averaging about three beats per minute, observed thirty minutes after injection.

Spasticity in Adults

Injection Site Reactions (e.g., pain, bruising, haemorrhage, erythema/haematoma etc.) have occurred following administration.

Upper Limb Spasticity in Adults

In double-blind studies, the most common adverse reactions observed (≥2%) in any DYSPORT dose group: 500 Units (N=197), 1000 Units (N=194) and more frequently than Placebo (N=279), respectively were: **Infections and infestations:** Nasopharyngitis (4%, 1%, 1%), Urinary tract infection (3%, 1%, 2%), Influenza (1%, 2%, 1%), Infection (1%, 2%, 1%); **Musculoskeletal and connective tissue disorders:** Muscular weakness (2%, 4%, 1%), Pain in extremity (0%, 2%, 1%), Musculoskeletal pain (3%, 2%, 2%), Back pain (1%, 2%, 1%); **Nervous system disorders:** Headache (1%, 2%, 1%), Dizziness (3%, 1%, 1%), Convulsion (2%, 2%, 1%), Syncope (1%, 2%, 0%), Hypoaesthesia (0%, 2%, <1%), Partial seizures (0%, 2%, 0%); **General disorders and administration site conditions:** Fatigue (2%, 2%, 0%), Asthenia (2%, 1%, <1%); **Injury, poisoning and procedural complications:** Fall (2%, 3%, 2%), Injury (2%, 2%, 1%), Contusion (1%, 2%, <1%); **Gastrointestinal disorders:** Diarrhea (1%, 2%, <1%), Nausea (2%, 1%, 1%), Constipation (0%, 2%, 1%); **Investigation:** Blood triglycerides increased (2%, 1%, 0%); **Respiratory, thoracic and mediastinal disorders:** Cough (1%, 2%, 1%); **Vascular disorders:** Hypertension (1%, 2%, <1%); **Psychiatric disorders:** Depression (2%, 3%, 1%)

Less Common Adverse Reactions: In a pooled analysis of clinical studies, adverse reactions (<2%) reported in DYSPORT treatment groups included dysphagia 0.5%, gait disturbance 0.5%, hypertonia 0.5%, and sensation of heaviness 0.3%.

Lower Limb Spasticity in Adults

Of the population exposed to DYSPORT (N=255), 89% Caucasian, 66% male, and median age was 55 years (range 23–77 years).

The most common adverse reactions (≥5%) in any DYSPORT dose group were falls, muscular weakness, and pain in extremity. Muscular weakness was reported more frequently in women (10%) treated with 1500 units of DYSPORT vs. men (5%). Falls were reported more frequently in patients ≥65 years of age. In a double-blind study, the most common adverse reactions

DYSPORT® (abobotulinumtoxinA) for injection, for intramuscular use
Brief Summary of full Prescribing Information (cont.)

observed (≥2%) in any DYSPORT dose group: 1000 Units (N=127), 1500 Units (N=128) and more frequently than Placebo (N=130), respectively were: **Musculoskeletal and connective tissue:** Muscular weakness (2%, 7%, 3%), Pain in extremity (6%, 6%, 2%) Arthralgia (4%, 2%, 1%), Back pain (3%, 0%, 2%); **Injury, poisoning and procedural complications:** Fall (9%, 6%, 3%), Contusion (2%, 0%, 0%), Wrist fracture (2%, 0%, 0%); **Nervous system disorders:** Headache (0%, 3%, 1%), Epilepsy/Convulsion/Partial seizure/Status Epilepticus (4%, 1%, 2%); **Infections and infestations:** Upper respiratory tract infection (2%, 1%, 1%); **General disorders and administration site conditions:** Fatigue (1%, 4%, 0%), Asthenia (2%, 1%, 1%), Influenza-like illness (2%, 0%, 0%), Edema peripheral (2%, 0%, 0%); **Investigations:** Alanine aminotransferase increased (2%, 0%, 1%); **Gastrointestinal disorders:** Constipation (0%, 2%, 1%), Dysphagia (2%, 1%, 1%); **Psychiatric disorders:** Depression (2%, 3%, 0%), Insomnia (0%, 2%, 0%); **Vascular disorders:** Hypertension (2%, 1%, 1%).

Lower Limb (unilateral or bilateral) Spasticity in Pediatric Patients (2 to 17 years of age; cerebral palsy)

In a double-blind study, the most common adverse reactions observed (≥4%) and reported more frequently than placebo, in patients who received placebo (N=79), Unilateral DYSPORT 10 units/kg (N=43), Unilateral DYSPORT 15 units/kg (N=50), Bilateral DYSPORT 20 units/kg (N=37), or Bilateral DYSPORT 30 units/kg (N=30), respectively were: **Infections and infestations:** Nasopharyngitis (5%, 9%, 12%, 16%, 10%), Upper respiratory tract infection (13%, 9%, 20%, 5%, 10%), Influenza (8%, 0%, 10%, 14%, 3%), Pharyngitis (8%, 5%, 0%, 11%, 3%), Bronchitis (3%, 0%, 0%, 8%, 7%), Rhinitis (4%, 5%, 0%, 3%, 3%), Varicella (1%, 5%, 0%, 5%, 0%), Ear infection (3%, 2%, 4%, 0%, 0%), Respiratory tract infection viral (0%, 5%, 2%, 0%, 0%), Gastroenteritis viral (0%, 2%, 4%, 0%, 0%); **Gastrointestinal disorders:** Vomiting (5%, 0%, 6%, 8%, 3%), Nausea (1%, 0%, 2%, 5%, 0%); **Respiratory, thoracic and mediastinal disorders:** Cough (6%, 7%, 6%, 14%, 10%), Oropharyngeal pain (0%, 2%, 4%, 0%, 0%); **General disorders and administration site conditions:** Pyrexia (5%, 7%, 12%, 8%, 7%); **Musculoskeletal and connective tissue:** Pain in extremity (5%, 0%, 2%, 5%, 7%), Muscular weakness (1%, 5%, 0%, 0%, 0%); **Nervous system disorders:** Convulsion/Epilepsy (0%, 7%, 4%, 0%, 7%)

Postmarketing Experience: Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use of DYSPORT: vertigo, photophobia, influenza-like illness, amyotrophy, burning sensation, facial paresis, hypoesthesia, erythema, and excessive granulation tissue. Hypersensitivity reactions including anaphylaxis have been reported.

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading.

Cervical Dystonia: About 3% of subjects developed antibodies (binding or neutralizing) over time with DYSPORT treatment.

Spasticity in Adults

Upper Limb Spasticity: From 230 subjects treated with DYSPORT and tested for the presence of binding antibodies, 5 subjects were positive at baseline and 17 developed antibodies after treatment. Among those 17 subjects, 10 subjects developed neutralizing antibodies. An additional 51 subjects from a separate repeat-dose study were tested for the presence of neutralizing antibodies only. None of the subjects tested positive. In total, from the 281 subjects treated in the long-term studies and tested for the presence of neutralizing antibodies, 3.6% developed neutralizing antibodies after treatment. In the presence of binding and neutralizing antibodies to DYSPORT some patients continue to experience clinical benefit.

Lower Limb Spasticity: From 367 subjects treated with DYSPORT and tested for the presence of binding antibodies, 4 subjects were positive at baseline and 2 developed binding antibodies after treatment. No subjects developed neutralizing antibodies. An additional 85 subjects from two separate studies were tested for the presence of neutralizing antibodies only. One subject tested positive for the presence of neutralizing antibodies. In total, from the 452 subjects treated in with DYSPORT and tested for the presence of neutralizing antibodies, 0.2% developed neutralizing antibodies after treatment.

Lower Limb Spasticity in Pediatric Patients: From 226 subjects treated with DYSPORT and tested for the presence of binding antibodies, 5 subjects previously receiving botulinum toxins were positive at baseline and 9 patients developed binding antibodies after injections. Among those 9 subjects, 3 subjects developed neutralizing antibodies, while one subject developed neutralizing antibodies from the 5 subjects testing positive for binding antibodies at baseline who previously received botulinum toxin injections. From a separate repeat-dose study, 203 subjects were tested for the presence of neutralizing antibodies. Two subjects were positive for neutralizing antibodies at baseline and 5 subjects developed neutralizing antibodies after treatments. In total, from the 429 patients tested for the presence of neutralizing antibodies, 2.1% developed neutralizing antibodies after treatment. In the presence of binding and neutralizing antibodies to DYSPORT, some patients continued to experience clinical benefit.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with DYSPORT. Patients treated concomitantly with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) should be observed closely because the effect of the botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of DYSPORT may potentiate systemic anticholinergic effects such as blurred vision. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of DYSPORT.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no adequate and well-controlled clinical studies with DYSPORT in pregnant women. DYSPORT should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. DYSPORT produced embryo-fetal toxicity in relation to maternal toxicity when given to pregnant rats and rabbits at doses lower than or similar to the maximum recommended human dose (MRHD) of 1000 Units on a body weight (Units/kg) basis.

Lactation: There are no data on the presence of DYSPORT in human or animal milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DYSPORT and any potential adverse effects on the breastfed infant from DYSPORT or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Infertility (Females)* In rats, DYSPORT produced adverse effects on mating behavior and fertility.

Pediatric Use

Cervical Dystonia and Upper Limb Spasticity: Safety and effectiveness in pediatric patients have not been established.

Lower Limb Spasticity in Pediatric Patients: The safety and effectiveness of DYSPORT injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients, or with lower limb spasticity below 2 years of age, have not been established.

Geriatric Use

Cervical Dystonia

There were insufficient numbers of patients aged 65 years and over in the clinical studies to determine whether they respond differently than younger patients. In general, elderly patients should be observed to evaluate their tolerability of DYSPORT, due to the greater frequency of concomitant disease and other drug therapy.

Adult Spasticity

Upper Limb Spasticity

Of the total number of subjects in placebo-controlled clinical studies of DYSPORT, 30% were ≥65 years of age, while 8% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Lower Limb Spasticity

Of the total number of subjects in placebo controlled clinical studies of DYSPORT, 18% (n = 115) were ≥65, while 3% (n = 20) were ≥75. Subjects aged ≥65 years who were treated with DYSPORT reported a greater percentage of adverse reactions as compared to younger subjects (46% vs. 39%). Fall and asthenia were observed with greater frequency in older subjects, as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

OVERDOSAGE: Excessive doses of DYSPORT may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle. Symptomatic treatment may be necessary. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis. There is no significant information regarding overdose from clinical studies.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at http://www.cdc.gov/ncidod/srp/drugs/drug-service.html.

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Innovation for patient care

Update on the Treatment of Batten Disease

A novel agent produced by recombinant DNA technology is indicated for treating motor progression associated with this neurodegenerative disease. Affected children must be identified as early as possible to provide the opportunity to attempt to slow disease progression with this new treatment.

Patricia McGoldrick, NP, MPA, MSN, and Steven Wolfe, MD

It is not unusual for clinicians to see children who have a speech–language delay respond to intervention. In a subset of children, however, language delay does not respond and may become worse; at times, continued language regression is associated with seizures and motor problems. The search for a cause then becomes crucial. When language delay occurs with seizures, the differential diagnosis includes neurodegenerative disorders and epileptic syndromes, such as Landau-Kleffner syndrome, glucose transporter type 1 (GLUT1) deficiency syndrome, myoclonic–astatic epilepsy (Doose syndrome), and one of the rarer causes of speech delay and regression, Batten disease, a fatal, inherited disease of the nervous system.

Batten Disease

The most severe of the neuronal ceroid lipofuscinoses—specifically, known as type 2 ceroid lipofuscinosis, neuronal (CLN2) or tripeptidyl peptidase 1 (TTP1) deficiency—Batten disease presents in childhood, usually between 3 and 4 years of age, when a typically developing child develops subtle problems, including clumsiness, behavioral issues, speech delay, seizures, and abnormal movements. Eventually, the child loses speech, vision, cognition, and the ability to walk, and becomes bedridden, blind, and demented. The disease is often fatal by the late adolescent years or early 20s.[1]

Batten disease is an autosomal recessive disorder caused by the absence or reduced activity of TTP1, leading to accumulation of lysosomal storage materials in the brain and resulting neuronal degeneration and death.[2] Typically, the disease does not manifest, and therefore is not suspected, until the child begins to have seizures and gait abnormalities at around age 3. Seizures can be atonic, generalized tonic–clonic, or myoclonic.

In the majority of cases, affected children have a preexisting speech delay that becomes worse at around the time that gait abnormalities and seizures develop. Subsequently, downward progression begins at 4 to 6 years of age, after which the child rapidly loses the ability to walk and becomes fully dependent by 10 to 12 years. Most children have a coexisting movement disorder, which becomes worse over time. Approximately two to four of every 1,000,000 live births in the United States are affected.[3]

Electroencephalographic findings in these children are significant for a photoparoxysmal response to low-frequency (1 to 2 Hz) photic stimulation. Brain MRI findings can include cerebellar atrophy and periventricular white-matter T2 hyperintensity. Genetic testing reveals 1) pathogenic mutations in each allele of the TPP1 gene (also known as the CLN2 gene) and 2) deficient TPP1 enzyme activity in leukocytes, fibroblasts, and dried blood spots.[4]

Progress on Therapy

No treatment was available to reverse Batten disease until recently: BioMarin Pharmaceuticals Inc. has developed a TPP1 enzyme replacement agent, cerliponase alfa (or rhTTP1; trade name, Brineura), that received FDA approval in April 2017. Administered directly into the brain by means of an intraventricular catheter (an Ommaya reservoir), cerliponase alfa works to slow the rate of neurological deterioration in Batten disease.

Cerliponase alfa is a purified human enzyme produced by recombinant DNA technology that is taken up by target cells in the central nervous system. The agent is translocated to neuronal lysosomes, where it is activated through the cation-independent mannose-6-phosphate receptor. The primary activity of this mature enzyme is the cleavage of N-terminal tripeptides from a range of protein substrates, allowing breakdown and degradation of the proteins and preventing storage and accumulation of unwanted proteins that cause Batten disease.[5]

Protocol for Administering Cerliponase Alfa

The recommended dosage of cerliponase alfa in patients age 3 and older is 300 mg administered in solution once every other week by intraventricular infusion. Administration is followed by an infusion of intraventricular electrolytes. The complete treatment takes approximately 4.5 hours. Pretreat-

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ment with antihistamines and with (or without) an antipyretic or corticosteroid is recommended 30 to 60 minutes before the start of infusion. The solution must be warmed at room temperature for 60 minutes before infusion.

Vital signs should be monitored before, during, and after infusion. Electrocardiography should be performed during infusion in patients who have a history of bradycardia, a conduction disorder, or structural heart disease (some patients with Batten disease have an associated conduction disorder or other cardiac disease.) In patients taking cerliponase alfa who do not have a cardiac abnormality, electrocardiographic evaluation should be performed every six months. In clinical studies, hypotension was reported in 8% of patients (during, or as late as eight hours after, infusion.)

Complications and Adverse Effects

Before infusion, the reservoir should be assessed for signs of acute intraventricular access device-related complications, including leakage, device failure, or signs of infection, such as swelling, erythema of the scalp, extravasation of fluid, or bulging of the scalp around or above the intraventricular access device. If a complication occurs during infusion, it should be discontinued.

Because symptoms of device-related infection might not be apparent, a cerebrospinal fluid specimen is usually sent for analysis before each infusion to detect subclinical device infection. In clinical studies of cerliponase alfa, intraventricular access device-related infection was rarely observed; when it was observed, antibiotics were administered, the intraventricular access device was replaced, and the patient continued cerliponase alfa treatment.

Other adverse events seen in clinical trials include:

- hypersensitivity reaction, including pyrexia, vomiting, pleocytosis, or irritability in 46% of the patients.
- seizures (atonic, generalized tonic-clonic, focal, and absence), reported in 50% of patients. (Seizures are common in patients with Batten disease, and are often the first presenting symptoms after speech delay.) In clinical trials, seizures were managed with standard anti-convulsive therapy and did not require discontinuation of cerliponase alfa.
- hematoma, reported in 21% patients, did not require treatment or interfere with cerliponase alfa infusion.[3]

Other Treatment Considerations

Before a child is approved for cerliponase alfa treatment, she (he) must have undergone genetic testing and functional gait analysis. Psychological, speech, occupational, and physical therapy evaluations are reviewed. An Ommaya reservoir must be placed, for administering intrathecal medication.

Response to medication and disease progression are monitored by the Motor domain of a CLN2 Clinical Rating Scale.[6] Because of the inability to establish comparability for the Language domain of the CLN2 Clinical Rating Scale, the efficacy of cerliponase alfa in the Language domain cannot be established.

Early Optimism, Continued Great Need

Children with Batten disease have concomitant learning disabilities, visual and swallowing problems, movement disorders, and gait abnormalities. Their needs include an accessible school environment, durable medical equipment, Social Security insurance, respite services, and home-care services.[7] A coordinated effort of pediatrics, neurology, social work, genetics, and pharmacy is needed to treat these children.

Although cerliponase alfa is indicated only for treating motor progression in Batten disease, it is hoped that its use will lead to more treatment options. Meanwhile, it is important for all clinicians to recognize the more unusual diagnoses that can manifest as seizures and speech delays. In the case of Batten disease, it is imperative that children be diagnosed as early as possible to provide the opportunity to attempt to slow disease progression. Specific abnormalities on electroencephalography and continued language regression are important clues that may lead to early diagnosis and treatment of Batten disease.

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A Call to Action for Early Diagnosis

The role of epilepsy gene panels in early diagnosis of CLN2 disease—a rapidly progressing pediatric neurodegenerative disorder

Until the onset of symptoms, children with CLN2 disease (a form of Batten disease) appear healthy.[1]

First symptoms classically present between the ages of 2 and 4 years and consist of language development delay, unprovoked seizures (epilepsy), and/or motor difficulty with clumsiness and ataxia.[1]

Because CLN2 disease is rare and typically presents with nonspecific early symptoms, patients endure an average delay in diagnosis of 2 years. During this time, symptoms worsen and function is lost.[2]

Loss of motor control and language ability occurs rapidly. Children commonly experience a complete loss of cognitive abilities, motor function, vision failure, and premature death.[1-3]

Given the rapid rate of progression, early diagnosis of CLN2 disease is critical.

CLN2 disease (neuronal ceroid lipofuscinosis type 2, also known as *TPP1* deficiency) is a neurodegenerative disease that primarily affects children and is caused by mutations in the *TPP1* gene (also referred to as the *CLN2* gene).[4-5]

Typically, due to lack of pursuing seizure etiology, misdiagnosis may occur as the early disease course is clinically similar to many other seizures and/or metabolic disorders, including: Ohtahara, West, Dravet, Lennox-Gastaut, myoclonic-astatic epilepsy/MAE (Doose syndrome), and Landau-Kleffner syndromes; GLUT1 deficiency; and benign myoclonic epilepsies.[5]

Laboratory diagnostics for CLN2 disease are well established and straightforward. Enzymatic and molecular testing can be diagnostic. The *TPP1* gene is included in many commercially available comprehensive epilepsy panels.[5]

More than 50% of epilepsies have some genetic basis, making early gene panel use one of the most direct, cost-effective, and accurate diagnostic tools.[6]

When Noah had his first seizure at 3, he could walk normally but his language was delayed. By the time he was diagnosed at age 5, he was unable to walk on his own and his language was unintelligible.

When you see the nonspecific signs of language development delay or motor difficulty with new onset unprovoked seizures, use genetic testing to help identify the cause of epilepsy before a patient experiences the hallmark signs of regression.

For more information about a no-cost epilepsy panel test, visit BehindTheSeizure.com

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Studies Examine CBD's Long-Term Safety and Efficacy in Treatment-Resistant Epilepsy

Researchers analyze data from phase III trials, an open-label extension study, and an expanded access program.

Among patients with treatment-resistant epilepsy, long-term add-on cannabidiol (CBD) therapy may reduce seizure frequency and be safe and generally well tolerated, according to studies presented in Washington, DC, at the 71st Annual Meeting of the American Epilepsy Society. In addition, seizure reduction may occur regardless of concomitant use of clobazam, which interacts with CBD, researchers said.

In previous phase III trials, investigators found that add-on CBD for 14 weeks, compared with placebo, reduces seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. In the present studies, researchers provided additional data and analyses from the clinical development program, including pooled data from phase III trials in Lennox-Gastaut syndrome, interim results from an open-label extension study, and data from an expanded access program.

The treatment, which is called Epidiolex, is a plant-derived pharmaceutical formulation of purified CBD in oral solution. Greenwich Biosciences, the US subsidiary of London-based GW Pharmaceuticals, is developing the drug. The company has submitted a New Drug Application to the FDA for Epidiolex as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.

Long-Term Efficacy in the Expanded Access Program

Since 2014, children and adults with severe treatment-resistant epilepsy have received CBD treatment as part of an expanded access program. The drug is made available through investigational new drug applications sponsored by individual physicians and states.

The program included children and adults who were receiving stable doses of antiepileptic drugs (AEDs) and were not candidates for clinical trials. During a four-week baseline period, parents and caregivers recorded seizures in a diary.

Patients received purified CBD (100 mg/mL) in oral solution at a gradually increasing dose from 2–10 mg/kg/day to tolerance limit or a maximum dose of 25–50 mg/kg/day, depending on site.

Martina E. Bebin, MD, Professor of Neurology at the University of Alabama at Birmingham, and colleagues presented pooled safety and efficacy data from the expanded access program through December 2016. The safety analysis included 607 patients with a median treatment duration of 338 days. The efficacy analysis included 580 patients.

Patients had a mean age of about 13, and 52% were male. Patients were taking a median of three concomitant AEDs at baseline. Median convulsive seizure frequency was 43 per 28 days, and median total seizure frequency was 72 per 28 days. Epilepsy etiologies included Lennox-Gastaut syndrome (15%); Dravet syndrome (10%); tuberous sclerosis complex (4%); Aicardi syndrome (3%); CDKL5 (3%); Doose, Dup15q, or febrile infection-related epilepsy syndromes (4%); other (40%); and unknown (20%).

The most common concomitant AEDs were clobazam (53%), levetiracetam (35%), and valproic acid (30%). Median CBD dose was 25 mg/kg/day at weeks 12 through 96.

After 12 weeks, add-on CBD was associated with 51% and 48% median reductions in monthly convulsive seizures and total seizures, respectively. The reduction was stable through 96 weeks. Fifty percent or greater, 75% or greater, and 100% response rates were notable and similar between time points, the researchers said.

"CBD was generally well tolerated," the researchers said. "Treatment-emergent adverse events were consistent with those reported previously.... Across the CBD development program, common adverse reactions are somnolence, decreased appetite, diarrhea, pyrexia, fatigue, lethargy, rash, nasopharyngitis, and pneumonia; dose-related reversible elevation of liver transaminases without elevation of bilirubin is an identified adverse reaction of special interest for CBD."

Of the 607 participants in the safety analysis set, 146 withdrew, including 89 for lack of efficacy and 32 due to

adverse events. Fifty-five percent of patients reduced their dose of CBD during follow-up.

Adverse events included diarrhea (29.2%), somnolence (22.4%), and pneumonia (10%). Abnormal liver adverse events (ie, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels greater than three times the upper limit of normal) were reported in 10% of patients.

Thirty-eight percent of patients on clobazam versus 14% of patients off clobazam had somnolence or sedation. Twelve patients died during the follow-up period. None of the deaths was considered related to treatment.

Expanded Access Program: Lennox-Gastaut Syndrome and Dravet Syndrome

Linda C. Laux, MD, Medical Director of the Comprehensive Epilepsy Center at the Ann and Robert H. Lurie Children's Hospital of Chicago, and colleagues examined pooled results for patients with Lennox-Gastaut syndrome or Dravet syndrome in the expanded access program through December 2016.

The safety analysis included 152 patients with a median treatment duration of 548 days. The efficacy analysis included 147 patients. Patients had a mean age of about 12.6, and about 60% were male. Patients' median convulsive seizure frequency was 41 per 28 days. Median total seizure frequency was 63 per 28 days.

Patients were taking a median of three concomitant AEDs at baseline. The most common AEDs were clobazam (66%), levetiracetam (43%), and valproic acid (34%).

Of the 152 participants in the safety analysis, 42 withdrew from the study, including 31 for lack of efficacy and five for adverse events.

Median CBD dose was 21 mg/kg/day at 12 weeks and 25 mg/kg/day at 96 weeks. Thirty-eight percent of patients reduced their dose of CBD during follow-up.

"Add-on CBD was associated with 50% and 44% reductions in median monthly convulsive [seizures] and total seizures, respectively, after 12 weeks; this reduction was stable up to 96 weeks," the researchers said. Response rates were notable and similar between time points. CBD was generally well tolerated, and treatment-emergent adverse events were consistent with those reported previously.

Abnormal liver adverse events were reported in 14% of patients.

The most common all-cause serious adverse events were convulsion (14%), status epilepticus (9%), pneumonia (5%), and pyrexia (4%). Thirty-eight percent of patients on clobazam versus 18% of patients off clobazam had somnolence or sedation. There were no deaths during the follow-up period.

Phase III Trials in Lennox-Gastaut Syndrome

In two phase III trials, add-on CBD treatment resulted in a greater reduction in drop, nondrop, and total seizures, compared with placebo, and was generally well tolerated. To provide additional insights across a larger patient population, Anup D. Patel, MD, Section Chief of Pediatric Neurology at Nationwide Children's Hospital in Columbus, Ohio, and colleagues presented pooled efficacy and safety outcomes from the studies.

In all, investigators randomized 235 patients to CBD and 161 to placebo. Patients had a mean age of about 15.5, and about 55% were male. Patients had failed a median of six AEDs and were taking a median of three AEDs at baseline.

In two phase III trials, add-on CBD treatment resulted in a greater reduction in drop, nondrop, and total seizures, compared with placebo, and was generally well tolerated.

Patients received the trial drug twice daily during a two-week titration period followed by a 12-week maintenance period.

Patients in the CBD 10-mg/kg/day group had a greater median percent reduction in drop seizure frequency per 28 days, compared with the placebo group (37.2% vs 17.2%) during the treatment period and during the maintenance period (40% vs 18.7%).

Patients in the pooled CBD 20-mg/kg/day group also had a greater median percent reduction in drop seizure frequency per 28 days (42.8% vs 20.1%) during the treatment period and during the maintenance period (48% vs 19.6%), compared with controls.

"During the maintenance period, drop seizure freedom was achieved by three patients (4%) in the CBD 10-mg/kg/day group, 10 (6%) in the CBD 20-mg/kg/day groups, and one (< 1%) in the placebo groups," the investigators said. "In both studies, 60% of patients and caregivers in the CBD

groups reported improvement in overall condition, as measured by the Subject/Caregiver Global Impression of Change (S/CGIC, versus 39% in the placebo groups."

Although adverse events were more frequent in patients receiving CBD than in those receiving placebo, CBD was generally well tolerated with few discontinuations and a safety profile similar to that observed in previous trials, the researchers said.

Dose-related elevations in transaminase enzyme levels were observed with CBD treatment, most commonly in patients receiving valproic acid and within the first month of treatment.

Treatment-related serious adverse events occurred in 3% of patients who received 10/mg/kg/day of CBD and 8.3% of patients who received 20 mg/kg/day. Adverse events leading to treatment discontinuation in more than one patient receiving CBD were increased ALT, AST, and γ-glutamyl transferase levels. One death was reported during the trial (acute respiratory distress syndrome in the CBD 20-mg/kg/day group). The death was deemed unrelated to treatment by the investigator.

Increases in ALT or AST occurred in three patients in the 10-mg/kg/day group, 31 patients in the 20-mg/kg/day groups, and one patient in the placebo group. Most of these patients (74%) were on valproic acid, and most elevations (63%) occurred within 30 days of treatment initiation. No patient met the standard criteria for drug-induced liver injury.

Thirty-four of the 35 increases in liver enzymes resolved. Elevations resolved spontaneously in 12 patients (four of whom were on valproic acid), following discontinuation in 13 patients (12 of whom were on valproic acid), and following dose reduction in nine patients (all of whom were on valproic acid). One patient was lost to follow-up.

Most Adverse Events Resolved

Michael Privitera, MD, Professor of Neurology at the University of Cincinnati and Director of the Epilepsy Center at the UC Neuroscience Institute, and colleagues examined CBD treatment effect and adverse events by time in the phase III trials in Lennox-Gastaut syndrome.

"A treatment difference emerged during the titration period and persisted to the end of treatment," the researchers said.

Onset of adverse events for most patients occurred during the titration period or the first four weeks of maintenance. Many adverse events resolved within four weeks of onset, and most resolved during the 14-week study period. Among patients with adverse events who received CBD, events resolved within four weeks of onset in almost 40% of patients and by end of study in more than 60% of patients.

> Long-term treatment with CBD was generally well tolerated, with a safety profile similar to that observed in the 14-week phase III trials.

Somnolence resolved within four weeks in 44% of patients and by end of study in 79% of patients. Decreased appetite resolved within four weeks in 35% of patients and by end of study in 70% of patients. Diarrhea resolved within four weeks in 60% of patients and by end of study in 77% of patients.

Open-Label Extension Study: Lennox-Gastaut Syndrome

Patients who completed the phase III trials in Lennox-Gastaut syndrome and Dravet syndrome were invited to enroll in an ongoing open-label extension study of CBD. Eric Marsh, MD, PhD, a pediatric neurologist at the Children's Hospital of Philadelphia, and colleagues examined maintenance of safety and efficacy in patients with Lennox-Gastaut syndrome in the open-label extension study. The date of data cutoff for this interim analysis was November 3, 2016.

The open-label study enrolled 366 patients with Lennox-Gastaut syndrome (mean age, 15.9; 54% male). Sixty-seven patients withdrew from the extension study, including 22 due to adverse events. Patients' median time on CBD treatment was 263 days.

"Long-term treatment with CBD was generally well tolerated, with a safety profile similar to that observed in the 14-week phase III trials," the researchers said. In addition, "long-term CBD resulted in sustained reductions in drop [seizure] and total seizure frequency. More than 80% of patients [or] caregivers reported improvements in overall condition versus baseline, as measured on the S/CGIC scale."

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Studies Examine CBD's Long-Term Safety and Efficacy in Treatment-Resistant Epilepsy

Continued from page 28

Increases in ALT or AST occurred in 37 patients, 29 of whom were on concomitant valproic acid. Thirty-four of 37 cases had resolved as of the data cutoff date. No patient had drug-induced liver injury.

Dravet Phase III Trials: Long-Term Open-Label Extension

Orrin Devinsky, MD, Director of the New York University Langone Comprehensive Epilepsy Center, and colleagues examined long-term safety and efficacy in patients with Dravet syndrome in the open-label extension study. In all, 264 patients from the phase III trials enrolled in the open-label extension study and were included in the safety analysis (mean age, 9.8; 50% male).

Efficacy data were based on the patients who enrolled from a completed phase III trial (GWPCARE1 part B). Patients who enrolled from a second, ongoing phase III trial (GWPCARE2) were not included in the efficacy analysis. The date of data cutoff for this interim analysis was November 3, 2016.

"Long-term treatment with CBD was generally well tolerated, with a safety profile similar to [that of] the 14-week phase III trial," the researchers said. It resulted in sustained reduction in convulsive seizure and total seizure frequency. More than 80% of patients/caregivers reported improvements in overall condition.

Seventy-five patients with Dravet syndrome withdrew from the extension study, including 17 due to adverse events.

Patients' median time on CBD treatment was 274 days. Mean dose of CBD was 21.17 mg/kg/day.

Serious adverse events considered treatment-related by the investigator and reported in more than 1% of patients were increased AST levels (1.9%) and status epilepticus (1.5%). "Of the four patients with serious treatment-related status epilepticus, three had changes in CBD or concomitant AED dose; all cases resolved, and patients continued on CBD," the researchers said.

Two patients died during the study. Both deaths were attributed to SUDEP and deemed unrelated to treatment.

Increases in ALT or AST more than three times the upper limit of normal occurred in 22 patients, all of whom were on concomitant valproic acid. Eighteen of the 22 cases had resolved as of the date of data cutoff. No patient met criteria for drug-induced liver injury.

Efficacy Regardless of Clobazam Treatment

Due to a bidirectional pharmacokinetic interaction between CBD and clobazam, Elizabeth A. Thiele, MD, PhD, Director of the Pediatric Epilepsy Program at Massachusetts General Hospital and Professor of Neurology at Harvard Medical School in Boston, and colleagues conducted a pooled post hoc analysis of CBD response and safety outcomes among patients on clobazam versus those off clobazam in the phase III trials. For comparison, the researchers also examined efficacy data by concomitant use of valproic acid, which has no known pharmacokinetic interaction with CBD.

"Add-on CBD treatment of seizures associated with Lennox-Gastaut syndrome resulted in clinically meaningful seizure reductions versus add-on placebo, regardless of concomitant use of clobazam or valproic acid," the researchers said. "Adverse events were reported more frequently in patients receiving CBD than in those receiving placebo, with more somnolence observed in patients on versus off clobazam."

The study is an analysis of nonrandomized subgroups, which limits the interpretability and generalizability of the results, the researchers noted.

—Jake Remaly

SUGGESTED READING

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A Conversation With Marshall Summar, MD

Based on an interview conducted by Ilona Kravtsova and Jennifer Nguyen

Marshall Summar, MD
Chairman of NORD's Board of Directors and
Director of the Rare Disease Institute at
Children's National Health System

Marshall Summar, MD, is the Director of the Rare Disease Institute at Children's National Health System, Washington, D.C. He joined Children's National in 2010 after spending 25 years at Vanderbilt University, Nashville, Tennessee. At Children's National, Dr. Summar is known for his pioneering work in providing care for children with rare diseases. In collaboration with the National Organization for Rare Disorders (NORD), he helped build the organization's patient-centered registry program, which maintains 17 disease-specific registries.

We posed questions to Dr. Summar about his efforts and the work of the Rare Disease Institute. Here is our report on the responses he gave.

Q. When did you become interested in rare diseases? What sparked your interest?

A. Dr. Summar's undergraduate training was in molecular biology. His interest in rare diseases was sparked in the mid-1980s, when he was in pediatric practice. Diagnosing and treating patients with a genetic condition has always been challenging from an intellectual standpoint, Dr. Summar said, and he has always been intrigued with the incredible variety that accompanies the thousands of rare diseases.

Q. What can you tell us about the Children's National Rare Disease Institute, where you are Director?

A. The Institute, which is the leader in the diagnosis and treatment of rare diseases and provides a medical home to rare disease patients and their families, is a first of its kind: NORD named it the first Center of Excellence of Clinical Care for Rare Diseases.

The Rare Disease Institute is "an answer to a need we created ourselves," Dr. Summar said. In other words, after advances in the diagnosis, treatment, and research of rare diseases, an entirely new cohort of patients came into existence. The art of diagnosis changed from what it had been 30 years earlier; with genome sequencing, clinicians could diagnose 6,000 to 7,000 diseases with great accuracy. Before, only about five FDA-approved therapies existed for patients with rare diseases; now, there are approximately 500. Treatments for rare diseases that were available 30 years ago were inadequate. Patients with Down syndrome, for example, did not survive past their 20s; now, patients survive well into their 50s. Another example: In the 1980s, only about 20% of patients diagnosed with a urea cycle disorder lived past 5 years. Now, survival past that age has increased to 95%.

With such dramatically improved survival, a new cohort of children with genetic-based rare diseases surviving into adulthood came to exist. Patients who transition from the pediatric to adult population find themselves in need of a medical home; the care model once limited to pediatrics must be centralized and extended to adult care. The Rare Disease Institute is equipped with

Continued on page 34

Ilona Kravtsova is a Doctor of Pharmacy Candidate (2019) at the Keck Graduate Institute, Claremont, California; holds a Certificate in Clinical Trials and Regulatory Affairs; and is President of the Keck Graduate Institute Student Chapter of the Rare Disease Club–NORD. Jennifer Nguyen is a Doctor of Pharmacy Candidate (2020) at the Keck Graduate Institute; holds a Certificate in Medication Therapy Outcome; and is Vice President of the Keck Graduate Institute Student Chapter of the Rare Disease Club–NORD.

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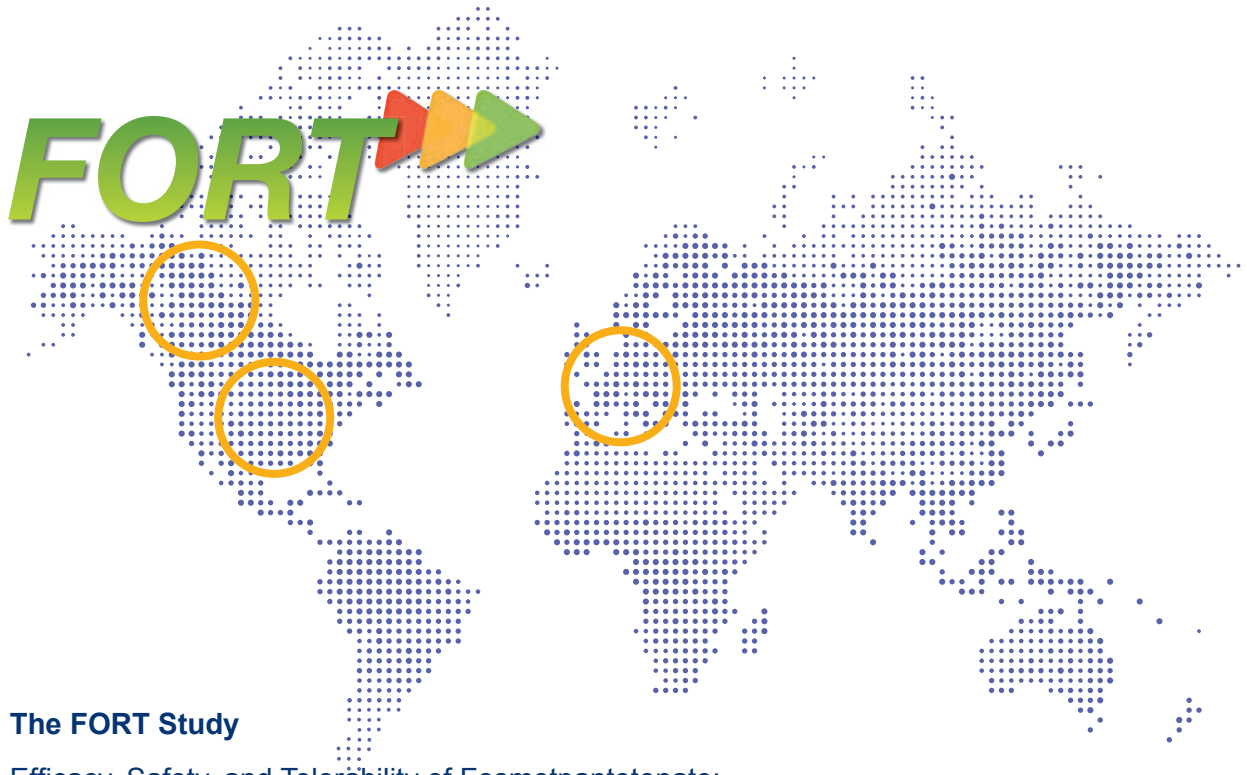

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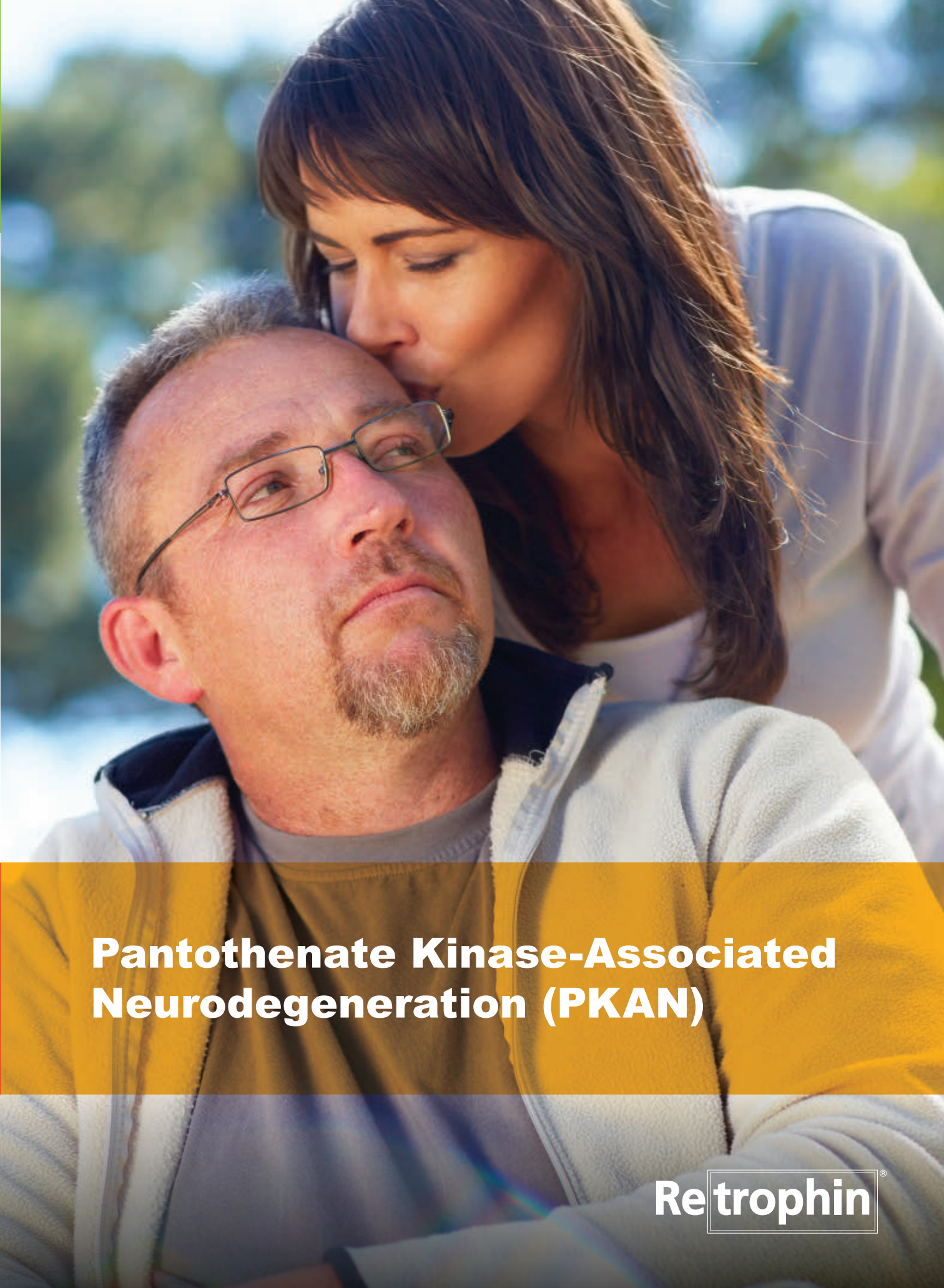
**Marshall R, Collins A, Escolar M, et al. Mov Disord 2017; 32 (suppl 2).



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A Conversation With Marshall Summar, MD

Continued from page 31

physicians and support staff trained in adult medicine and in genetics.

The time has come to treat rare diseases as a lifespan issue.

Q. What can you tell us about Rare Disease Centers of Excellence and the role they have in diagnosis and treatment?

A. With the increasing number of rare-disease patients who are surviving, it is simply "the right time," Dr. Summar said, to create Centers of Excellence across the nation. The NORD partnership with those centers will bring standardization to the field. Those national standards can then be used to develop other centers.

The purpose of NORD's model, the first Center of Excellence at the Children's National Health System Rare Disease Institute, is to, first, develop standards for the diagnosis and care of rare diseases and, second, disseminate this information across platforms. Under NORD's oversight, a three-tier system of centers will be created across the United States in the hope of eliminating gaps in care. These centers, Dr. Summar said, will "provide predictability, safe spaces for patients and their families, and a way to move forward"—and enhanced quality of life.

The three-tier system is based on the amount of resources and a willingness to be part of a network and to contribute to it.

- **Level-1 centers** will provide full service—all the expertise and resources necessary to take care of patients with rare diseases.
- **Level-2 centers** are application-based; any hospital and university can reach out and apply, but standards for acceptance will be high. These centers will specialize in rare disease groups. Some centers will have full expertise about specific diseases, but will not have a comprehensive reach. Some will have the resources and capacity to become a level-1 center, and all centers will be in geographically advantageous areas.
- **Level-3 centers** will have the expertise for specific rare diseases. All level-3 centers will be equipped with robust diagnostic teams; advancements in diagnosis will be a big component.

Q. Where do you see treatments for rare diseases in five years?

A. Within five years, Dr. Summar believes, to establish best practices with rare-disease therapies, physicians need to advance their diagnostics and chronic management to draw near pharmaceuticals. Pharmaceutical companies develop new therapies for a disease, but there is still a gap between diagnosis and therapy that must be consolidated. Dr. Summar believes that diagnostics should advance along with orphan drugs.

Many rare diseases have a genetic cause; Dr. Summar sees an increase in the pace of advancement, in the near future, in gene therapy. One such therapy involves transfer of nucleic acids, including DNA and RNA.

The study of rare-disease progression and subsequent development of therapies is changing. Dr. Summar thinks that the biggest impact in the next 5 years will be creation of *natural history registries.* Typically, there are two ways to understand a disease. A cross-sectional study collects data on an entire study population, at defined intervals; this method is appropriate when examining a chronic disease, such as diabetes, in the lifespan, but is unsuitable for understanding rare diseases because of a lack of data and a small population. A rare disease might only affect five or 10 patients, and new methods for understanding the disease must be created to accommodate this population, however small. A natural history registry allows medical researchers to document the course of disease, study progression and response to treatment, and fill in gaps in knowledge. Once again, "patients become the best teachers," Dr. Summar points out.

The purpose of NORD's model, the first Center of Excellence at the Children's National Health System Rare Disease Institute, is to, first, develop standards for the diagnosis and care of rare diseases and, second, disseminate this information across platforms.

Dr. Summar believes that "the most important thing on the current horizon is the NORD registry" of the natural

history of rare diseases. In this scheme, a disease-specific advocacy organization partners with NORD to create a patient-centered registry. A main component of the project is dissemination of information across various advocacy groups and healthcare professionals. The data generated will be incredibly useful across the rare-disease space, ranging from information for clinical studies to expanding knowledge on clinical outcomes and the natural history of diseases. Already, a handful of diseases have been entered in the standardized registry system, and further documentation of natural history data will elevate understanding of rare diseases, their variables, and progression.

Q. What is your greatest challenge when working with children who have a rare disease?

A. One of the greatest challenges in properly treating a patient with a rare disease is that there are just not enough data and literature for physicians. A lack of resources and information becomes a barrier to care. Also, no two children are alike, even when they have the same rare disease. This makes standardization of treatment difficult.

Dr. Summar acknowledged another challenge that arises when working with children who have a rare disease. Often, a child is diagnosed with a disease that no one has ever heard of; this creates a feeling of isolation for the patient. One of the reasons that Dr. Summar is a supporter of NORD is that the organization breaks though that isolation, and the stigmatization, while maximizing quality of life for patients and their families.

Q. Do you have a most memorable patient encounter?

A. In 1986, a young man with a rare disorder of the urea cycle led Dr. Summar, who had been the man's pediatrician, to pursue a rewarding and fulfilling research career. He described how this happened: After visiting this patient's bedside in the intensive care unit, Dr. Summar learned that no research had been performed on the urea cycle disorder. For the next 25 years, a deficient enzyme in the urea cycle became one of his primary research foci.

"That particular patient taught me more than what I ever did for him," Dr. Summar said. "Rare-disease patients are the best teachers."

Although Dr. Summar has seen approximately 26,000 patients during the course of his career, he remembered, and was able to describe, his most memorable patient encounter.

Q. What would you say, in closing, about the study of rare diseases, and the care of these patients?

A. Dr. Summar believes that physicians who specialize in rare diseases are closer to their patients than physicians are in any other medical specialty. They must work very closely with patients' families, and it is the patients who are the driving force behind the processes of study and care.

The creation of Rare Disease Centers of Excellence across the United States is a pivotal step in meeting an unmet medical need—and in advocating for, diagnosing, and treating patients with rare diseases.

The Refractory Epilepsy Screening Tool for Lennox-Gastaut Syndrome:

A New Assessment Instrument That May Be Useful for the Identification of Patients With Lennox-Gastaut Syndrome

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Lennox-Gastaut syndrome (LGS) is a progressive epileptic encephalopathy with no known cure.[1] Patients with LGS experience frequent, persistent, intractable seizures,[2,3] and LGS is associated with a substantial negative impact on the lives of patients and their caregivers.[4] At onset, developmental delays are frequently present (20%–60% of patients), and the condition is associated with progressive cognitive deterioration, with approximately 75% to 95% of patients having intellectual impairments after five years.[1] Comorbid neuropsychiatric disturbances and behavioral issues (eg, aggression, hyperactivity, and autistic characteristics) also may occur.[1,5] Although patients with LGS experience a variety of seizure types, drop attacks occur in approximately half of patients and are of particular concern.[1,6,7] These abrupt and sudden falls occur without warning and pose risk of injury. Consequently, patients prone to these events may wear helmets with facemasks as a protective measure,[6,7] and some may require a wheelchair because of gait disturbances or drop attacks.[2] Because LGS can profoundly impair cognitive, social, and physical functioning, patients may need constant care throughout their lives and may not be able to attend mainstream schools, work, or live independently.[4,6-9] For patients with LGS, treatment goals include attempting to control seizures and improving quality of life by use of antiepileptic medications along with nonpharmacologic measures (eg, ketogenic diet, vagus nerve stimulation, surgical interventions such as resection or corpus callosotomy).[10]

Although the progressive and severe nature of LGS makes the accurate and early diagnosis of the condition essential for optimal management, it is considered one of the most challenging obstacles.[5] LGS most commonly manifests during early childhood (typically before 8 years of age and most frequently between 3–5 years of age); however, sometimes LGS may remain undiagnosed until patients are adolescents or adults.[1,3] The clinical diagnosis of LGS classically includes the identification of a triad of features: cognitive impairment, multiple seizure types (tonic, atonic, and atypical absence), and abnormal electroencephalogram (EEG) findings, including slow generalized spike-waves while awake and paroxysmal fast activity during non–rapid eye movement sleep.[1,5] Nevertheless, recognition and diagnosis may be complicated by a variety of factors, including the numerous potential etiologies (eg, pathologic conditions affecting the brain, such as abnormal development, injury, infection, or tumor; genetic components), variable clinical presentations (eg, multiple types of seizures experienced, differing EEG features over time), and the lack of definitive biologic markers.[1,10,11] In addition, the key features of LGS tend to change as the disease progresses, especially as patients become older (eg, the slow spike-wave pattern on EEG may diminish or disappear).[6]

> To aid clinicians in the identification of patients with LGS, the Refractory Epilepsy Screening Tool for LGS (REST-LGS) was developed.

To aid clinicians in the identification of patients with LGS, the Refractory Epilepsy Screening Tool for LGS (REST-LGS) was developed.[12] Using a set of eight clinical

criteria initially identified by an expert group via modified Delphi consensus methodology (Table 1), a validation study was conducted by a retrospective evaluation of 200 records of patients with refractory epilepsy at two sites. In a diagnosis-blinded chart review by both an epilepsy specialist and nonspecialist care provider, the inter-rater reliability showed moderate to very good agreement for all major criteria and three of four minor criteria. Following this initial precision assessment, the patient diagnosis data were unblinded, and it was determined that the majority of patients with an LGS diagnosis met three major and two to three minor criteria. In contrast, individuals with a non-LGS drug-resistant epilepsy diagnosis met one or fewer major and one to two minor criteria. These findings suggest that the REST-LGS has potential as a useful clinical screening instrument that can allow both expert and nonexpert care providers to identify patients who may benefit from further evaluations for the diagnosis of LGS.

TABLE 1. Criteria of the Refractory Epilepsy Screening Tool for Lennox-Gastaut Syndrome[12]

Major Criteria	Minor Criteria
• ≥2 seizure types	• Persistent seizures despite use of ≥2 antiepileptic drugs
• Seizure onset before 12 years of age	• History of vagus nerve stimulation, ketogenic diet, or epilepsy surgery
• History of EEG with generalized slow spike-wave discharges (<2.5 Hz)	• Other EEG abnormalities (eg, multifocal spikes, generalized discharges, paroxysmal fast activity)
• Cognitive impairment since childhood	• Evidence of seizure-related helmet use or head or face injuries

EEG=electroencephalogram.

Currently, LGS is considered a rare epilepsy disorder (in the United States, estimated new diagnoses total 250 children each year)[13]; however, under-recognition and misdiagnosis may be common because of heterogeneity and evolution of clinical features.[3,5] More efficient diagnostic procedures and earlier intervention may lead to improved outcomes for patients with LGS, including reduction in the frequency of seizures and improvement in quality of life. Further, accurate diagnosis may enable better overall access to care by allowing patients to meet payer coverage criteria. The REST-LGS may prove to be a simple yet valuable clinical screening instrument for LGS.

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Update on Pharmacotherapy for Epileptic Encephalopathies

These rare pediatric epilepsy syndromes, often refractory to treatment, are a hotbed of research, including gene therapy and gene-editing technology, aimed at trying to reduce their significant morbidity and mortality.

Russle Benson and Vivek Banapur

Epileptic encephalopathies are a significant clinical challenge in neurology. These disorders are rare pediatric epilepsy syndromes characterized by severe seizures that begin in infancy or early childhood and cause neurocognitive and behavioral deficits.[1] Although individually rare, in aggregate epileptic encephalopathies may cause as many as 40% of seizures that occur during the first three years of life.[1] These disorders include West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, early myoclonic encephalopathy, myoclonic status in nonprogressive encephalopathies, malignant migrating partial seizures of infancy, epilepsy with continuous spike-and-waves during slow-wave sleep, Landau-Kleffner syndrome, Ohtahara syndrome, Rasmussen's encephalitis, and Doose syndrome.[2]

Management of epileptic encephalopathies is complicated by the fact that these disorders often have many comorbidities and are refractory to treatment. In recent years, there has been a wealth of research investigating epileptic encephalopathies; new techniques in metabolic imaging and genomic analysis have granted critical insights into their pathogenesis. Current research focuses most heavily on West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome; investigators have elucidated several advances in the understanding and the potential treatment of these disorders, as we discuss here.

West Syndrome

Also known as infantile spasms, West syndrome is an epileptic encephalopathy that may constitute as many as 2% of childhood epilepsies; as many as 50% of patients with seizure onset in the first year of life may suffer from West syndrome.[3] When West syndrome is recognized, it is often between 4 to 8 months of age.

West syndrome is characterized by clusters of brief myoclonic seizures and a distinct electroencephalogram (EEG) pattern called hypsarrhythmia,[4] which is an abnormal interictal pattern consisting of disorganized, chaotic electrical activity with high-amplitude waves and spikes that occur irregularly. West syndrome is usually classified as cryptogenic and symptomatic:

- **Symptomatic West syndrome** can be attributed to an identified cause, such as perinatal hypoxic–ischemic injury. Symptomatic cases of West syndrome have, historically, had a worse prognosis than cryptogenic cases.
- **Cryptogenic West syndrome** does not have an identifiable cause.[5] As understanding of the etiology of West syndrome has grown, fewer cases are labeled cryptogenic—because fewer are attributed to an unknown cause.[5]

Terminology. A shift in classification is needed to better categorize subgroups of West syndrome. In 2010, the International League Against Epilepsy (ILAE) Commission on Classification and Terminology proposed classifying West syndrome as genetic, structural, metabolic, and unknown etiologic, replacing symptomatic and cryptogenic etiologic groups.[5] Other recently proposed subgroups include West syndrome due to metabolic disease, cytomegalovirus infection, and tuberous sclerosis.[5] In addition, several genes have recently been associated with West

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Mr. Benson and Mr. Banapur are Doctor of Pharmacy candidates at Keck Graduate Institute School of Pharmacy, Claremont, California.

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Update on Pharmacotherapy for Epileptic Encephalopathies

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syndrome *(ARX, CDKL5, FOXG, GRIN1, GRIN2A, MAGI, MEF2C, SLC25A22, SPTANI, STXBP1, KCNB1, SCN8A* and 15q11-q13[5-7]); their discovery may lead to new genetic classifications of subgroups of West syndrome in the future.

Therapeutics. In all cases of West syndrome, timely diagnosis and prompt treatment are central to reducing the neurocognitive damage caused by seizures. Only two drugs are approved by the FDA for the treatment of West syndrome: adrenocorticotropic hormone (ACTH) and vigabatrin (trade name, Sabril; Lundbeck). High-dose ACTH (150 IU/m^2) has been shown to control infantile spasms in greater than 50% of patients, and there is mounting evidence to suggest that low-dose ACTH (20-40 IU/m^2) may be equally efficacious in controlling spasms.[5] Vigabatrin has been shown to be somewhat less efficacious than ACTH in treating infantile spasms, and carries a major risk of causing permanent visual-field loss that results in tunnel vision.[5] For these reasons ACTH is often preferred over vigabatrin; however, vigabatrin has demonstrated superior efficacy in treating infantile spasms associated with tuberous sclerosis.[5] Levetiracetam, nitrazepam, valproate, topiramate, and zonisamide are also used, but only add-on therapy in severe, refractory cases. Pyridoxine may be useful in treating rare cases of infantile spasms caused by vitamin B_6 deficiency.[5]

Results of recent studies have suggested that high-dose oral prednisolone (40-60 mg/d) and ACTH may be similarly efficacious; a 2015 ILAE consensus document endorsed prednisolone as a treatment option that is "probably" effective for West Syndrome.[8] If prednisolone exhibits real-world efficacy, it is likely that it will become a favored agent in the treatment of West syndrome because it is readily available and inexpensive.

Other new studies have begun to explore the utility of the mammalian target of rapamycin (mTOR) inhibitors rapamycin and everolimus to treat infantile spasms associated with cortical malformations, such as infantile spasms due to the tuberous sclerosis complex. Results from the EXIST-3 phase III, randomized, double-blind, placebo-controlled trial demonstrated that adjunctive everolimus significantly reduces seizure activity for patients with tuberous sclerosis complex and treatment-resistant epilepsy.[9]

Last, recent results from The International Collaborative Infantile Spasms Study (ICISS) found combined treatment with steroids and vigabatrin to be more effective than monotherapy, suggesting a potential place for polytherapy with hormonal agents and vigabatrin in the treatment of West syndrome.[10]

Lennox-Gastaut Syndrome

The epileptic encephalopathy Lennox-Gastaut syndrome (LGS) constitutes as many 10% of cases of childhood epilepsy.[11] LGS is usually diagnosed between 3 to 5 years of age and presents with cognitive dysfunction, an EEG slow spike-and-wave pattern (<2.5 Hz), and multiple types of seizures (including tonic, atonic, atypical absence, focal myoclonic, and generalized tonic-clonic).[11] Affected children often suffer serious injury from frequent drop attacks caused by atonic seizures.

Lennox-Gastaut syndrome is related to West syndrome, with as many as 20% of cases having a history of West syndrome.[11] Similar to West syndrome, the etiology of LGS is often classified as cryptogenic and symptomatic. Cryptogenic LGS is of unknown cause; symptomatic LGS has an identifiable cause, including genetic, structural, and metabolic abnormalities.[11] Recent genetic studies have associated LGS with possible gene mutations in *GABRB3, ALG13, SCN8A, STXBP1, DNM1, FOXG1,* and *CHD2.*[12] Variability in the presentation of LGS makes it a challenging disorder to diagnose; early diagnosis and treatment are critical, however, for management to be effective.

Variability in the presentation of LGS makes it a challenging disorder to diagnose; early diagnosis and treatment are critical, however, for management to be effective.

Therapeutics. Valproate is considered by most clinicians and authorities to be the drug of choice for LGS.[11] It is thought that valproate potentiates GABA (γ-aminobutyric acid)-ergic inhibitory effects; interacts with metabolism of γ-hydroxybutyrate, a metabolite of GABA; suppresses N-methyl-D-aspartate (NMDA)-evoked depolarization; and inhibits Na+ channels.[13] Perhaps these multiple mechanisms of action are what make valproate useful in the treatment of many types of seizures.

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MICKIE'S MIRACLES

Infantile Spasms Case Study:

What One Survivors' Mom Wants You To Know

by Kristie Griess

Stop for a moment and imagine your beautiful little baby girl is three months old. Now imagine her eyes rolling back into her head and her body becoming ridged and trembling as a seizure takes hold.

That's exactly what happened to our little girl Mickie on an early morning in January 2012. Leading up to this she was sweet and amiable until becoming extremely irritable days before her first seizure. In a terrifying 24-hours, Mickie would have five more seizures while we were ambulanced from one hospital to the next. Shockingly, Mickie was diagnosed with Infantile Spasms (IS), a catastrophic form of pediatric epilepsy

She immediately started ACTH injections, one of the two IS treatments recognized in the American Academy of Neurology journal, co-authored by the Child Neurology Society. To our dismay, the spasms returned six weeks after the injections stopped. Mickie's neurologist emphasized that Vigabatrin, the second approved drug, could cause peripheral vision damage. He stressed this side effect so much that we started her on the ketogenic diet with devastating results. Mickie's spasms increased to 60 a day and went on to fail eight anti-seizure medications over nine months.

My maternal instincts told me my daughter's life was in peril. Her spasms were physically subtle, imperceptible to most, with strange movements of the arms, legs and eyes. Many pediatricians will only see two cases of IS in their entire career. This is why we are blessed that Mickie's first seizures were so dramatic we took immediate action. We learned intractable epilepsy can cause cortical blindness, severe cognitive impairment and death. Also, children that fail two or more anti-seizure drugs have a 90 percent chance of failing all anti-seizure drugs. Luckily, we received a referral to a Pediatric Epileptologist at a level four epilepsy center where Mickie would be evaluated for brain surgery. The day before Mickie's first birthday, surgeons removed her left side parietal, occipital and temporal lobes and stopped her seizures. After five years and thousands of hours of therapy, her right brain has compensated. She sings, dances, swims and spends more than half of her school day in a mainstream first grade class. Mickie is a living miracle and her future is bright!

This journey inspired me to launch Mickie's Miracles, a nonprofit dedicated to global pediatric epilepsy awareness. We are committed to educating parents and pediatricians on the signs, symptoms and urgency needed to identify and treat IS. A baby's brain is precious and too fragile to let a single day pass without fighting to stop IS.

Join us at
MickiesMiracles.org

Update on Pharmacotherapy for Epileptic Encephalopathies

Continued from page 40

Valproate alone is rarely sufficient, however, to provide adequate control of seizures; polytherapy with other anti-epileptic drugs is often needed. Other anti-epileptic drugs indicated for the treatment of LGS are felbamate, lamotrigine, topiramate, rufinamide, clonazepam, and clobazam. In a recent post-hoc analysis of the CONTAIN trial, clobazam used in conjunction with either valproate, lamotrigine, levetiracetam, or topiramate was found to result in significant seizure control for patients with LGS.[14]

Interim analysis of the recent phase III placebo-controlled GWPCARE 3 and GWPCARE 4 trials found that cannabidiol may be an efficacious add-on therapy to help significantly reduce seizure frequency in LGS.[15] Importantly, cannabidiol research has also determined that the drug is a potent inhibitor of cytochrome P450 (CYP) enzymes, including CYP3A4 and CYP2C19; clinicians therefore need to be vigilant in screening for possible drug–drug interactions when using cannabidiol in combination with other agents.[16]

Dravet Syndrome

Also known as severe myoclonic epilepsy of infancy, Dravet syndrome is an epileptic encephalopathy that begins in the first year of life in an otherwise healthy infant. The disorder is often diagnosed before 12 months of age.[17] It is characterized by prolonged febrile and non-febrile seizures in a child and frequent episodes of status epilepticus.[17] Patients often have multiple comorbidities, including intellectual disability, behavior and sleep problems, and crouch gait.[18] Patients also have an increased risk of sudden unexpected death in epilepsy, with more than 50% of patients experiencing premature mortality (before 10 years of age).[18]

More than 70% of cases of Dravet syndrome are thought to be caused by de novo nonsense mutations in the *SCN1A* gene that codes for the NaV1.1 sodium channel.[17] In addition, mutations in *SCN1B, SCN2A, GABRG2, PCDH19,* and *CHD2* have also recently been associated with Dravet syndrome.[19] As with any epileptic encephalopathy, prompt diagnosis and treatment are key for a positive outcome.

Therapeutics. Dravet syndrome is unique—not only because the disorder is refractory to treatment but because so many antiepileptic drugs are contraindicated. It is now recognized that sodium channel-blocking drugs, such as phenytoin, fosphenytoin, carbamazepine, oxcarbazapine, eslicarbazepine, lamotrigine, and rufinamide should be avoided because these drugs may exacerbate seizures in Dravet syndrome.[18] Vigabatrin and tiagabine should also generally be avoided because they present the risk of aggravating myoclonic seizures.[20]

First-line treatment of Dravet syndrome is valproate, due to its broad spectrum of anti-seizure activity, although polytherapy with multiple antiepileptic drugs is usually needed.[18] Clobazam is often the first choice added to valproate; clobazam is also considered a first-line agent for treating Dravet syndrome.[18]

Second-line agents include topiramate, levetiracetam, and, possibly, stiripentol.[18] The latter is a unique agent approved in Europe, Canada, and Japan as adjunctive therapy, with clobazam and valproate, for Dravet syndrome, based on the results of two randomized, controlled trials.[21] Stiripentol is one of the few agents with significant evidence to support its efficacy in treating Dravet syndrome, but obtaining the drug in the United States is challenging because it is not FDA-approved. Lack of access to stiripentol limits clinicians' ability to provide effective pharmacotherapy.

Drugs on the horizon for the treatment of Dravet syndrome are fenfluramine, lorcaserin, and cannabidiol. Fenfluramine, also known as ZX008, is an investigational drug believed to release serotonin by disrupting vesicular storage and reversing serotonin transporter function. Early results from studies of fenfluramine have shown that the drug has the potential to produce strong, sustained control of seizures in Dravet syndrome.[22,23]

In another recent study, the serotonergic agonist lorcaserin was able to successfully reduce seizure activity in a small, uncontrolled trial of five patients with Dravet syndrome.[24]

Last, a recent multicenter, open-label study of 25 patients with Dravet syndrome who received greater than 99% pure, oil-based cannabidiol extract demonstrated that the drug reduced seizure frequency by 63%; 16% of patients achieved complete remission of seizures.[25]

Summing Up and Future Directions

Epileptic encephalopathies are a group of rare pediatric epilepsy syndromes that cause cognitive deficits and are refractory to treatment. These disorders are the target of a hotbed of research aimed at trying to reduce their significant morbidity and mortality.

As understanding of these disorders grows, novel therapeutic targets are constantly being sought out. As genetic

causes of epileptic encephalopathies are discovered, gene therapy and gene-editing technology, such as CRISPR/Cas9, may provide powerful new treatment options. Although much remains to be discovered about how to treat epileptic encephalopathies, new research and new therapies will continue to improve outcomes and quality of life for these patients.

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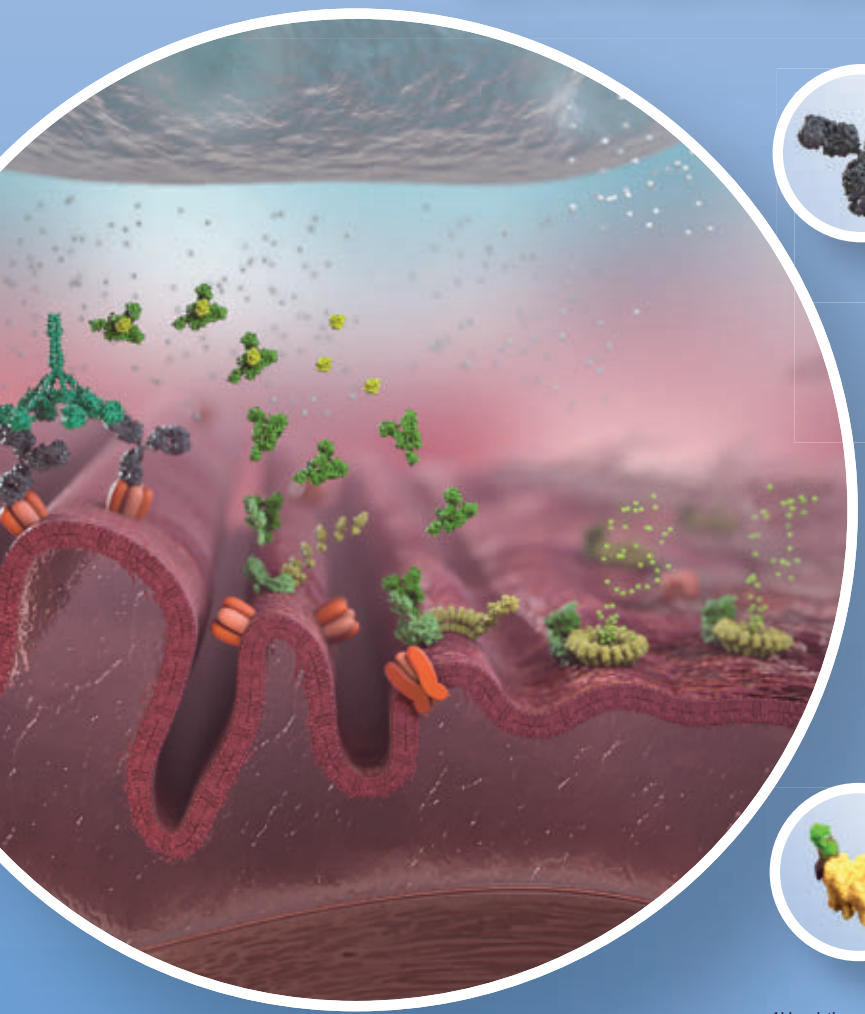
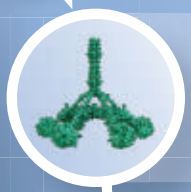
COMPLEMENT-MEDIATED DESTRUCTION OF THE NMJ OCCURS IN MANY PATIENTS WITH ANTI-AchR+ gMG[1]



Autoantibodies to the acetylcholine receptor (AchR) are detected in **up to 88% of gMG cases**



C1q
Anti-AchR autoantibodies bind to AchRs, triggering C1q binding

COMPLEMENT CASCADE INITIATED

C5a and C5b
Cleavage of the C5 protein activates the terminal complement pathway

C5b to C9 (TCC)
TCC damages the postsynaptic membrane, causing muscle damage and weakness

Abbreviations: NMJ, neuromuscular junction; TCC, terminal complement complex.

Indications and Usage
Generalized Myasthenia Gravis (gMG)
Soliris is indicated for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.

Important Safety Information

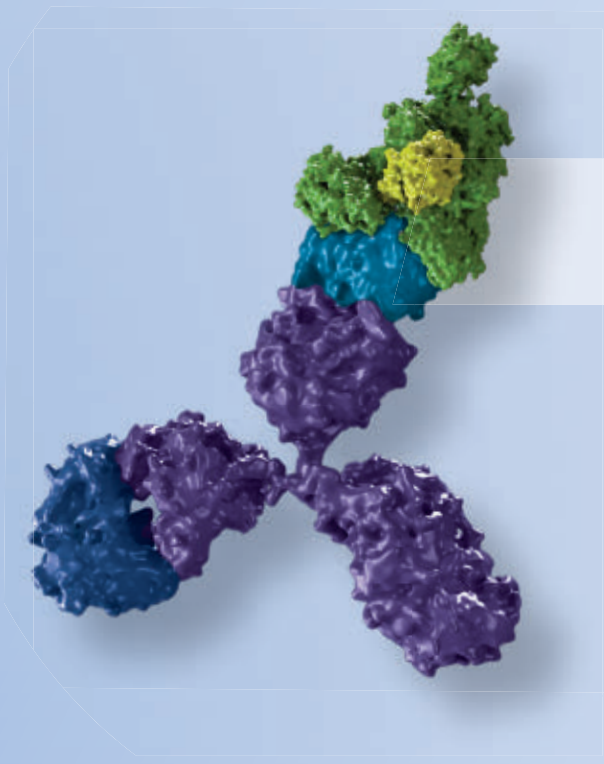
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris.
Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection.**
- **Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

Please see additional Important Safety Information on the following page and accompanying Brief Summary of full Prescribing Information.



SOLIRIS® (eculizumab) IS A COMPLEMENT INHIBITOR[2]

Soliris binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b, preventing the formation of the TCC.

The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown but is presumed to involve reduction of TCC C5b-9 deposition at the NMJ.[2]

Soliris is the first and only terminal complement inhibitor approved for the treatment of adult patients with anti-AchR+ gMG.[3]

See what the first therapy approved in more than 60 years[4] for MG could mean for your patients with anti-AchR+ gMG at Soliris.net/MG

Important Safety Information (continued)

Contraindications
Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection

Warnings and Precautions
Other Infections
Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection.

Infusion Reactions
Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

Adverse Reactions
The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain.

Please see full Prescribing Information including boxed WARNING regarding serious meningococcal infection at www.Soliris.net.

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ALEXION®

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

SOLIRIS® (eculizumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early [*see Warnings and Precautions (5.1)*].

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].**
- **Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program [*see Warnings and Precautions (5.2)*]. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

1 INDICATIONS AND USAGE

Soliris is indicated for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS [*see Warnings and Precautions (5.2)*].

Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection [*see Warnings and Precautions (5.1) and (5.2)*].

Only administer as an intravenous infusion.

2.3 Recommended Dosage Regimen – gMG

For patients with generalized Myasthenia Gravis, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

2.4 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

For adult patients with gMG, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI) (Table 2).

Table 2: Supplemental Dose of Soliris after PE/PI

Type of Plasma Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each Plasma Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

2.5 Preparation

Dilute Soliris to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed Soliris 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses (Table 3).

Table 3: Preparation and Reconstitution of Soliris

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.

Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25° C, 64-77° F]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.6 Administration

Do Not Administer As An Intravenous Push or Bolus Injection
Administer the Soliris admixture by intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 h at 2-8° C (36-46° F) and at room temperature.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg single-dose vials each containing 30 mL of 10 mg/mL sterile, colorless, preservative-free eculizumab solution.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis).

Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible.

In prospective clinical studies, 75/100 patients with atypical hemolytic uremic syndrome (aHUS) were treated with Soliris less than 2 weeks after meningococcal vaccination and 64 of these 75 patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving Soliris have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 2 out of 196 paroxysmal nocturnal hemoglobinuria (PNH) patients developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated [*see Adverse Reactions (6.1)*]. In clinical studies among non-PNH

patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with Soliris [*see Adverse Reactions (6.1)*].

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

5.2 Soliris REMS

Because of the risk of meningococcal infections, Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccine(s).

Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

5.3 Other Infections

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection [*see Warnings and Precautions (5.1)*].

5.6 Infusion Reactions

Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections
- Other Infections
- Monitoring Disease Manifestations After Soliris Discontinuation
- Thrombosis Prevention and Management
- Infusion Reactions

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris. In PNH clinical studies, two patients experienced meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in one unvaccinated patient. Meningococcal sepsis occurred in one previously vaccinated patient enrolled in the retrospective aHUS study during the post-study follow-up period [*see Warnings and Precautions (5.1)*].

Generalized Myasthenia Gravis (gMG)

In a 26-week placebo-controlled trial evaluating the effect of Soliris for the treatment of gMG (gMG Study 1), 62 patients received Soliris at the recommended dosage regimen and 63 patients received placebo. Patients were 19 to 79 years of age, and 66% were female. Table 8 displays the most common adverse reactions from gMG Study 1 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than placebo.

Table 8: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in gMG Study 1 and at a Greater Frequency than in Placebo-Treated Patients

Adverse Reaction	Soliris (N=62) n (%)	Placebo (N=63) n (%)
Gastrointestinal Disorders		
Abdominal pain	5 (8)	3 (5)
General Disorders and Administration Site Conditions		
Peripheral edema	5 (8)	3 (5)
Pyrexia	4 (7)	2 (3)
Infections and Infestations		
Herpes simplex virus infections	5 (8)	1 (2)
Injury, Poisoning, and Procedural Complications		
Contusion	5 (8)	2 (3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in the long-term extension to gMG Study 1, Study ECU-MG-302, that are not included in Table 8 were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

6.2 Immunogenicity

As with all proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to eculizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of antieculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the aHUS indication, as well as for additional patients with PNH. In the PNH population, antibodies to Soliris were detected in 3/196 (2%) patients using the ELISA assay and in 5/161 (3%) patients using the ECL assay. In the aHUS population, antibodies to Soliris were detected in 3/100 (3%) patients using the ECL assay. An ECL based neutralizing assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 3 patients with aHUS and the 5 patients with PNH with positive samples using the ECL assay. Two of 161 patients with PNH (1.2%) and 1 of 100 patients with aHUS (1%) had low positive values for neutralizing antibodies. None of 62 patients with gMG had antibodies to Soliris detected immediately following the 26-week active treatment.

No apparent correlation of antibody development to clinical response was observed.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Soliris. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Soliris exposure.

Cases of serious or fatal meningococcal infections have been reported.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Alexion's PNH and aHUS disease registries collect pregnancy outcomes in women exposed to Soliris during pregnancy. To enroll or to obtain information, contact www.pnhregistry.com or www.ahusregistry.com, or call (215)-616-3558. In cases where gMG patients become pregnant, call (215)-616-3558.

Risk Summary

There are no available data on Soliris use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

8.2 Lactation

Risk Summary

There is no information regarding the presence of eculizumab in human milk, the effects on the breastfed infant, or the effects on milk production. IgG is excreted in human milk, so it is expected that eculizumab will be present in human milk. However, published data suggest that antibodies in human milk do not enter the neonatal and infant circulation in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Soliris and any potential adverse effects on the breastfed child from Soliris or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of Soliris for the treatment of PNH in pediatric patients have not been established.

The safety and effectiveness of Soliris for the treatment of aHUS have been established in pediatric patients. Use of Soliris in pediatric patients for this indication is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS. The studies included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult patients [*see Adverse Reactions (6.1), and Clinical Studies (14.2)*].

The safety and effectiveness of Soliris for the treatment of generalized Myasthenia Gravis in pediatric patients have not been established.

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis, Streptococcus pneumonia* and *Haemophilus influenza* type b (Hib) according to ACIP guidelines [*see Warnings and Precautions (5.1, 5.2, 5.3)*].

8.5 Geriatric Use

Forty-five patients 65 years of age or older (15 with PNH, 4 with aHUS, and 26 with gMG) were treated with Soliris in clinical trials in the approved indications. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Prior to treatment, patients should fully understand the risks and benefits of Soliris, in particular the risk of meningococcal infection. Ensure that patients receive the Medication Guide.

Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccines use while on Soliris therapy. Inform patients that vaccination may not prevent meningococcal infection [*see Warnings and Precautions (5.1)*].

Signs and Symptoms of Meningococcal Infection

Inform patients about the signs and symptoms of meningococcal infection, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given a Soliris Patient Safety Information Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other Infections

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Inform parents or caregivers of children receiving Soliris for the treatment of aHUS that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) according to current medical guidelines.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation.

Inform patients with aHUS that there is a potential for TMA complications due to aHUS when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following Soliris discontinuation. Inform patients who discontinue Soliris to keep the Soliris Patient Safety Information Card with them for three months after the last Soliris dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of Soliris.

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NEUROLOGY REVIEWS

Myasthenia Gravis

Challenges and Burdens of Disease

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Pathophysiology of Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder mediated by autoantibodies that bind to targets in the postsynaptic membrane of the neuromuscular junction and cause skeletal muscle weakness.[1] Multiple distinct subtypes have been identified clinically and immunopathologically, and these can differ in primary immune targets, clinical presentation, and response to treatment strategy.[1,2]

Carr et al estimated a pooled incidence rate of 5.3 per million person-years based on 35 studies performed between 1950 and 2007, and a pooled prevalence of 77.7 cases per million based on 44 studies from that time period.[3] However, the authors cite an extremely wide variation in each set of results.[3]

While the absolute estimates may vary, the prevalence of MG has been increasing due to improved diagnostics as well as to medical advances that have increased lifespan.[4] The yearly incidence has also been increasing according to recently published studies, with a pronounced increase in both older males as well as in females, even after adjustment for life expectancy.[4]

What has also become increasingly apparent is the variety of autoantibodies implicated in MG. The most common subtype of MG is caused by antibodies directed at acetylcholine receptors (AChR MG).[2,4] These patients may have follicular hyperplasia (up to 70% of this group), thymomas (about 10% of group), or a normal or atrophic thymus gland.[2]

The clinical subclassifications of AChR MG include early- or late-onset generalized disease, associated with thymoma, and ocular MG, as well as a more recently added classification for clustered AChR.[2,5]

- In early-onset AChR MG, patients typically have IgG1 and IgG3 antibodies directed against AChR. Early-onset disease is more common in females than males,[2] with onset before age 50.[5] Patients are more likely to have thymic hyperplasia than thymic atropy or have no thymic pathology.[2]
- Late-onset AChR MG also involves IgG1 and IgG3 antibodies, with age at onset ≥50 years, either normal or atrophic thymic tissue,[2] and a male > female predominance.[6]
- Thymomatous AChR MG involves both IgG1 and IgG3 antibodies and neoplasia of the thymous.[2] Thymoma can be found in about 10% to 15% of patients with MG.[5]
- About 15% of patients with MG have only ocular signs and symptoms; about half of these patients have detectable AChR antibodies.[1] Some have antibodies to clustered AChR.[2]
- Clustered AChR MG is caused by IgG1 antibodies that test negatively for AChR antibodies in conventional radioimmunoprecipitation assays but test positive in a cell-based assay.[2] Disease may be less severe in these patients, and they may have thymic hyperplasia.[2] Previously these individuals had been included in the AChR antibody-negative groups.

Three mechanisms have been described that produce MG symptoms in these patients: (1) antibody binding to AChR with subsequent complement activation and endplate lysis; (2) cross-linking of AChR by antibodies that causes the AChR to be internalized and degraded; and (3) direct binding of ACh binding sites by the antibodies that in turn blocks ACh access to these sites.[2]

Other individuals with MG do not have AChR antibodies and were initially lumped together in a category known as

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seronegative MG. Some have now been found to have autoantibodies directed at other targets. These include antibodies to a postsynaptic protein known as muscle-specific kinase (MuSK), which accounts for 1% to 10% of MG patients depending on ethnicity.[1,4,5,7] Anti-MuSK antibodies are primarily IgG4, which do not activate complement.[4] Other autoantibodies have been identified in patients with MG in the absence of AChR or MuSK antibodies; these include antibodies directed against lipoprotein-related protein 4 (LRP4), and agrin.[4] The causality of these autoantibodies is being carefully studied, with further characterization of disease phenotype ongoing.

Treatment Resistent MG

Conventional therapies for MG include acetylcholinesterase inhibitors (AChEI), plasmapheresis, intravenous immunoglobulin (IVIg), corticosteroids or other immunosuppressive agents, and thymectomy.[8] Some patients do not respond to these therapies and are classified as refractory (or resistant) to treatment; much of the literature refers to this as refractory MG.

However, the terms refractory/resistant have not been universally defined for individuals with MG, and the clinical definitions vary somewhat in the literature. For example, Suh and colleagues refer to patients with MG who are refractory to treatment as those who cannot reduce immunotherapy, specifically steroids, without clinical relapse, who have inadequate response to immunosuppressive therapy, or who develop severe side effects to immunosuppressive medications.[8] Silvestri and Wolfe specify similar criteria but also add "requirement of excessive amounts of potentially harmful agents; presence of comorbidities that preclude the use of conventional treatments; requirement for repeated rescue treatment with short-term therapies . . . and/or frequent myasthenic crises."[9] A consensus definition has now been specified in the 2016 international consensus guidance for the management of MG, which defines refractory MG as "Post-Intervention Status (PIS) classification is unchanged or worse after corticosteroids and at least 2 other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician."[10]

The actual prevalance of patients who are not adequately treated is unknown, in part because these patients are rare.[9] Based on prespecified criteria, Suh et al identified 109 nonrefractory patients with MG and an additional 19 who were resistant to treatment over 7.5 years of clinical experience in a US medical center.[8]

In the US study, the refractory group had a younger median age of onset of disease (36 vs 60 years; $P<.001$) compared with the nonrefractory group, and a greater proportion of the refractory group were female (74% vs 47%; $P=.03$).[8] Antibody status was known for 90% of the patients. While a nominally smaller percentage of refractory patients had anti-AChR antibodies (53%) than the nonrefractory group (75%), the P value for this difference was .05. A larger percentage of the refractory group had anti-MuSK antibodies (47% vs 2% of the nonrefractory group; $P<.001$). Of those who had antibody status available for review, none of the refractory group were negative for both anti-AChR antibodies and anti-MuSK antibodies, as compared with 23% of the nonrefractory group ($P=.02$). Looking at these data more carefully, while MuSK MG patients were more likely to be refractory, there was actually a slightly higher total number of AChR MG patients in this group (10/19). Overall, 81.8% of the MuSK group vs 12.2% of the AChR group met prespecified refractory criteria. The authors also compared thymectomy and thymoma status. A higher percentage of refractory patients (68%) received thymectomy than the nonrefractory group (17%; $P<.001$). Thymoma status was available for about 60% of the patients; 45% of the refractory group had thymomas versus 14% of nonrefractory patients ($P=.02$).[8]

A few treatment options have been explored for patients who are resistant to standard treatment protocols. Rituximab, a monoclonal antibody that binds to and depletes B cells, was used in 6 small series summarized by Silvestri et al in a 2014 review of refractory MG.[9] Most patients experienced some degree of clinical improvement.[9] A more recent study concluded that it appears to be an effective option with sustained long-term benefit after treatment in patients with refractory AChR MG.[11] A multicenter, prospective, placebo-controlled clinical trial in patients with generalized AChR+ MG is currently under way.[12]

A recent multicenter, blinded, prospective review provided Class IV evidence that for MuSK MG, rituximab increased the probability of a favorable outcome.[13]

The actual prevalance of patients who are not adequately treated is unknown, in part because these patients are rare.

A 2008 study investigated high-dose cyclophosamide to "reboot" the immune system in a small patient population.[14] This treatment targets mature immune cells but does not affect hematopoietic stem cells. The drug was largely tolerable and clinical improvement was shown in most patients.[14] The authors suggested follow up treatment with conventional immunosuppressants.

Thymectomy has long been a mainstay treatment for myasthenia gravis, based on limited data supporting its benefit. A 2016 multicenter, placebo-controlled, randomized trial showed thymectomy to be a viable option to improve clinical outcomes in patients with MG and allow for a reduced need for immunosuppressive therapy.[15] It is important to note that this trial was conducted in patients with generalized AChR MG, not specifically targeting a refractory population.

As targeted therapeutics begin to be applied to the management of patients with refractory MG, it is critical that we not only better understand the distinct immunopathologic differences between disease subtypes, but also that

neurologists be aware of these in order to make best medical practice decisions in the care of their patients.

Burden of Disease

MG is associated with a high burden of disease to the individual patients, including hospitalization and outpatient visits, daily medications, effects on activities of daily living, quality of life, and working life and income. It also affects family members and caregivers.

Hospitalizations, outpatient visits, daily medications

For patients with MG, both hospitalizations and multiple outpatient visits can significantly impact their lives. The number of reported hospitalizations, outpatient visits, and medications will vary by stage of disease and recommended treatment at a given time in a given country. Nevertheless, the data demonstrate a serious burden for typical patients with MG. For example, among a group of 113 US patients with MG that were identified from health care claims data, 14 had a total of 38 hospital admissions during the calendar year 2009, while 83 had a total of 578 outpatient visits during the same time period.[16] Many patients with MG require one or more daily medications as well. Among a cohort of 1288 MG patients identified from US insurance claims records from 2008-2010, 80% had claims for AChEI and 51% for opioid analgesics, 79% were prescribed some sort of oral immunosuppressive therapy, 19% took at least 2 types of immunosuppressive therapies, 12% received IVIg, and 3% received plasma exchange therapy.[17]

Effects on daily living

MG affects basic functions of daily living such as chewing, and swallowing, which in turn impact eating and nutrition, and, therefore, weight. The disease impairs other motor activities such as walking. It can also lead to drooping eyelids, difficulties with vision and speech, and arm and leg weakness. All of these can affect not only the individual's activities of daily living, but also important aspects of family life and professional life. There is a large psychological impact as well, with patients facing cessation of their careers, the prospect of causing financial and social stress to their families/caregivers, and social isolation.[18] Patients may also experience myasthenic crisis, which refers to difficulty in breathing that leads to hospitalization and need for medical ventilation, which can be life-threatening.[18]

In Australia, the Centre for International Economics (CIE) published the first comprehensive report on the burden of MG to patients and the community, summarizing the responses of 190 people with MG.[19] Eighty-eight percent of respondents had experienced symptoms of MG in the preceding 12 months, especially general fatigue (73%), hand or arm weakness (68%), and leg weakness (65%).[19] Eight percent had symptoms serious enough to require a ventilator for breathing at least once in the preceding year, while 19% reported at least one lifetime event requiring ventilator use.[19]

A survey in Germany also describes the serious impact of MG on basic aspects of daily living. More than 75% of individuals with MG had limited mobility due to muscle weakness after physical strain, with 70% describing problems in walking.[20] More than 40% reported dysphagia, approximately 39% reported problems with chewing or defecation, 38% reported ptosis, and 37%, diplopia.[20] Speech disorders, neck weakness, and problems with facial expression each affected more than one quarter of the respondents.[20] Additional symptoms included miction problems, sexual disorders, and muscle weakness even at rest (17% to 25% of respondents).[20]

MG is associated with a high burden of disease to the individual patients, including hospitalization and outpatient visits, daily medications, effects on activities of daily living, quality of life, and working life and income.

Health-related quality of life measures

Surveys in a number of countries have assessed the effect of MG on health-related quality of life (HRQOL) using the SF-36 instrument, which measures 8 domains, including physical functioning, problems with physical activities, pain, general health, vitality (perceived energy), social functioning, emotional health impact on activities, and mental health (mood).[20] The survey of German patients, for example, indicated that HRQOL is low, primarily due to impaired mobility and depression.[20] Similar results were reported in a study of patients from Norway and the Netherlands.[21] A study conducted in Serbia reported that more severe disease, poor acceptance of the disease, and higher levels of anxiety and depression were predictors of worse HRQOL.[22] A study from China also cited the impact of anxiety and depression on worsening HRQOL, and the authors concluded that both the physical and mental QOL domains were negatively impacted.[23]

Effect of MG on working life and income

Studies from across the globe show that MG leads to a reduction in work hours or forced transfers or long-term unemployment with a marked impact on income and productivity. Japanese patients with MG, for example, report unemployment (27%), forced transfers at work (4%), and a decline in income (36%).[24] Nearly half of those reported that their income had been cut by at least 50%.[23] In a Danish population, MG was associated with a 6-fold higher risk of unemployment and a 9 times higher risk of long-term sick leave (9 or more weeks) 2 years after diagnosis, compared with the general population.[25] In Australia, MG affected work performance (69% of respondents) and choice of occupation (45%), and led to change of occupation (33%). Of those reporting sick leave due to MG in the previous year, 24% reported sick leave duration of 2 to 8 weeks and 27% reported taking leave for more than 8 weeks (27%), indicating significant productivity losses due to MG.[19]

The 2013 CIE report quantified financial losses; Australian patients, who cited a reduction in work hours that averaged 5.5 hours per week, reported average income losses of $41,505 per patient per year.[19] The average drop in income levels was 39%, with a 16% reported average decline in asset levels.[19]

Impact on caregivers

The Australian report also describes the impact of MG on the caregivers of patients with MG, who often must assist them with daily activities. One-third of patients with MG describe, for example, difficulty with driving due to vision problems or arm weakness.[19] Additionally, patients described difficulty with doing the laundry (58%), lifting and carrying objects (70%), walking upstairs (67%), cleaning bathrooms (55%) and vacuuming (53%).[19] As a result, nearly one-third of patients reported needing help with daily activities, and almost half of those individuals required continuous care.[19] Usually the major provider for those requiring assistance is the spouse or partner, with only 5% reporting primary source of care to be another family member, friend, or professional caregiver.[19]

Burden of disease in treatment-refractory patients with MG

Current assessments of the burden of disease in MG do not separate nonrefractory from refractory patients. However, because multiple treatment failures and myasthenic crises form the definition of refractory disease, patients who are not adequately treated likely experience an even higher burden than as compared with average patients described in these reports, including additional treatment costs as well as physical and psychological impacts of multiple treatment failures. Additional studies are needed to better understand this population.

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Cerebrotendinous Xanthomatosis: A Treatable Inherited Lipidosis

Once the cause of cerebrotendinous xanthomatosis—a defect and deficiency of chenodeoxycholic acid—is identified, replacement therapy inhibits abnormal bile-acid synthesis and restores the impermeability of the blood–brain barrier..

Gerald Salen, MD

Cerebrotendinous xanthomatosis (CTX; Online Mendelian Inheritance in Man [OMIM] #213700) is a rare autosomal disorder of bile-acid synthesis caused by a mutation in the cytochrome P450 *CYP27A1* gene that results in a defective sterol 27-hydroxylase enzyme. An abnormally high level of cholestanol, the 5-alpha-dihydro derivative of cholesterol, accumulates in plasma and is deposited with elevated cholesterol in the brain, tendon xanthomas, and bile.

There is marked variability from patient to patient in the signs and symptoms, severity, and age of onset in CTX. Hallmark clinical manifestations include early-onset chronic diarrhea, bilateral juvenile cataracts, tendon and tubular xanthomas, and progressive disabling neurologic dysfunction. The course of disease is disabling and includes intellectual disability, autism, behavioral and psychiatric problems, and dementia.

Etiology

CTX is caused by mutations in *CYP27A1* that result in production of a defective sterol 27-hydroxylase enzyme. CYP27A1 is a mitochondrial enzyme that is ubiquitously expressed, and is responsible for catalyzing multiple hydroxylation reactions in cholesterol and bile-acid metabolism and synthesis, including 27-hydroxylation of bile-acid intermediates in the classic synthetic pathway. In CTX, impairment in CYP27A1 activity, in combination with a limited ability to cleave the cholesterol side-chain by the alternative microsomal bile acid synthetic pathway, results in diminished cholic acid formation and almost no production of chenodeoxycholic acid (CDCA). Consequently, increased quantities of C-27 bile alcohols are formed and excreted as glucuronides in the urine.

In addition, upregulation of cholesterol synthesis and enhanced production of cholestanol lead to increased plasma levels of cholestanol and accumulation of cholestanol and cholesterol in tissues throughout the body, notably the brain (white matter), lens, and tendons. Deposition in these tissues results in, respectively, neurologic dysfunction, cataracts, and tendon xanthomas, all of which are characteristic of CTX. In patients with CTX, cholestanol accounts for as much as 10% of sterols in xanthomas, 10% of sterols in bile, and as much as 50% of sterols in the brain.

Although the exact mechanism by which cholestanol accumulates in the brain is unknown, some data suggest that the blood–brain barrier may be impaired in patients with CTX—specifically, the observation that cholestanol and apolipoprotein B concentrations are increased in the cerebrospinal fluid of patients with CTX indicates enhanced permeability of the blood–brain barrier. It has been suggested that such increased permeability may be a result of damage caused by circulating bile alcohol glucuronides.

More than 99 mutations implicated in CTX have been identified, including missense mutations, deletions, insertions, splice site mutations, and nonsense mutations. No correlation has been established with specific mutations and specific clinical features or disease severity (i.e., no genotype–phenotype correlation). In addition, phenotypic variation within families and among persons with the same mutations has been reported.

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Presentation

Cerebrotendinous xanthomatosis is a rare disease that has been observed more frequently among females than males (approximately 55%, compared to approximately 45%, respectively). Moreover, clinical expression appears earlier and with greater severity among males than among females. Disease progression is usually slow, with diverse clinical presentations that can encompass a varied combination of neurologic and non-neurologic manifestations. Onset is as early as infancy and as late as adulthood. Clinical hallmarks include premature bilateral cataracts (88% of patients), intractable diarrhea (approximately 50%), progressive neurologic signs and symptoms (pyramidal, 77%; cerebellar, 62%), and tendon xanthomas (69%).

Neurologic dysfunction is the most disabling feature of CTX. Neurologic symptoms are an important clinical hallmark of CTX, are present in many cases at diagnosis, and distinguish CTX from other lipid disorders (e.g., familial hypercholesterolemia and sitosterolemia). A broad range of neurologic findings has been reported in CTX patients: low intelligence, pyramidal signs (e.g., spasticity, hyperreflexia, and extensor plantar responses), cerebellar signs (e.g., ataxia, dysarthria, and nystagmus), peripheral neuropathy, dementia, psychiatric symptoms, autism, seizures, and parkinsonism.

Neurologic manifestations generally emerge during adolescence or early childhood and become worse over time; developmental delays, intellectual disability, cognitive impairment, and learning difficulties, on the other hand, may emerge during childhood.

Additional clinical features associated with CTX have been described:

- **Osteoporosis,** with an increased risk of bone fracture, is often present in adult patients, despite normal levels of serum calcium, phosphate, and vitamin D metabolites
- **Premature atherosclerosis** has been reported, although plasma cholesterol is generally not elevated
- **Pulmonary manifestations and xanthomas of the lungs** have been reported.

Diagnosis and Testing

CTX is diagnosed on the basis of clinical findings, biochemical testing, neuroimaging, and molecular genetic analysis. The clinical presentation can vary considerably in type, severity, and timing of symptoms. Onset of symptoms generally occurs during childhood or adolescence (age at onset, 9 to 19 years), but diagnosis does not occur until adulthood—a considerable delay in diagnosis. Among the factors that result in this delay are a variable presentation and a resemblance to other conditions, including multiple sclerosis, peripheral neuropathy, mental retardation, and cerebellar ataxia.

Several biochemical features characterize CTX:

- **The cholestanol concentration** in plasma and tissues is elevated, particularly in the brain, tendons, and bile; this finding can be used for diagnosis
- **Bile-alcohol glucuronides** are excreted in urine, bile, and plasma at elevated levels.

Monitoring bile acid and alcohol profiles in bile, plasma, and urine is useful as a measure of the effectiveness of CDCA treatment.

Treatment

CDCA replacement represents the standard of care for treating patients with CTX. Following the discoveries in CTX patients that 1) biliary bile acid is abnormal and 2) there is a near-absence of CDCA, oral administration of CDCA (10 mg/kg/d) was evaluated and shown to correct biochemical abnormalities and alleviate clinical symptoms.

Most importantly, CDCA restores blood–brain barrier impermeability. Xanthomas, however, xanthomas do not usually diminish. The beneficial effects of CDCA treatment on neurologic manifestations and function are generally greater when treatment is started earlier, (suggesting that damage due to deposition of cholesterol and cholestanol in nerve tissues may be reversible), thus preventing irreversible multi-organ damage and onset of clinical symptoms.

Alternative treatments for CTX have been examined: hydrophilic bile acids, cholestyramine, clofibrate, statins alone or in combination with CDCA, and low-density lipoprotein apheresis. All have shown limited efficacy in inhibiting abnormal bile acid synthesis, reducing or maintaining already reduced cholestanol levels, and reducing the severity of clinical symptoms.

Surgical removal of xanthomas is not recommended (unless a xanthoma puts pressure on a nerve or the blood supply) because tissue injury leads to rapid reformation of the xanthoma.

Summary

Although CTX is rare, the disease can be treated effectively. The first step is to recognize the defect and deficiency of CDCA. Next, replacement therapy inhibits abnormal bile-acid synthesis and restores the impermeability of the blood–brain barrier.

Genetic Testing: MDA Paves the Way for Better Care in Limb-Girdle Muscle Weakness

Since the launch of the Muscular Dystrophy Association's genetic testing program in 2015, nearly 3,000 people have been tested for 35 genes that cause known LGMD subtypes or other diseases that can cause similar symptoms—and utilization is increasing while plans to expand the program unfold this year.


Lianna R. Orlando, PhD, and Grace K. Pavlath, PhD

Several neuromuscular diseases can present with limb-girdle muscle weakness and wasting of the shoulder and pelvic girdle muscles, which pose a diagnostic challenge for physicians seeking to treat their patients appropriately. Given this significant phenotypic overlap, a clinical diagnosis is not enough in these cases. Genetic analyses are needed to more efficiently, and accurately, identify the underlying cause of disease—thus improving diagnostic efforts and disease management in larger numbers of patients. With the advent of ever-improving (and more affordable) genetic technologies, as well as increased research efforts and awareness have come major breakthroughs in the identification, classification, and understanding of the genetic aberrations underlying limb-girdle muscle weakness.

Overview

The limb–girdle muscular dystrophies (LGMD) are a group of genetically heterogeneous neuromuscular diseases, with more than 30 genetically defined subtypes of varying severity. In addition, other diseases, such as Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy (EDMD), Bethlem myopathy, and late-onset Pompe disease (glycogen storage disease type II), can manifest with an LGMD-like phenotype.

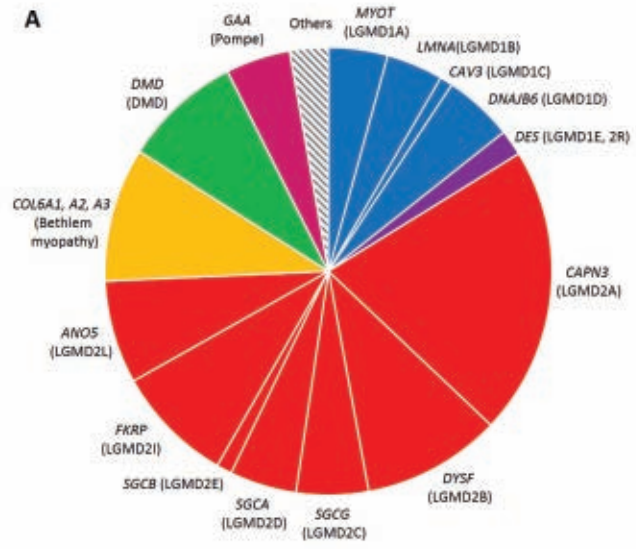
Because all of these diseases are seen in Muscular Dystrophy Association (MDA) neuromuscular clinics, MDA is in a unique position to facilitate genetic testing for people and families seeking a more definitive diagnosis. In 2015, as part of this effort and with support from Sanofi Genzyme, MDA launched a program that provides free screening of a panel of genes known to cause limb-girdle muscle weakness to patients seen at MDA clinics.

Why Genetic Testing?

The benefits of prompt and accurate genetic diagnosis are significant. Foremost, genetic testing informs care management, long-term prognosis, and family planning. Some diseases, such as DMD and late-onset Pompe disease, have FDA-approved therapies that are effective at relieving symptoms and slowing disease progression. Some diseases that cause limb–girdle muscular weakness, including some of the LGMD subtypes, also involve cardiac and respiratory muscles; having the appropriate genetic diagnosis is critical to improving preemptive management and increasing monitoring of cardiac and respiratory complications.[1] Having a genetic diagnosis also allows patients to participate in research studies and clinical trials and enter a registry, as well as seek support

Dr. Orlando is the Scientific Program Officer, and Dr. Pavlath is the Senior Vice President and Scientific Director at the Muscular Dystrophy Association in Chicago, Illinois.

A



B

GENE	%
CAPN3 (LGMD2A)	20.9
DYSF (LGMD2B)	10.1
COL6A1, A2, A3 (Bethlem)	9.7
FKRP (LGMD2I)	8.6
DMD (DMD)	8.6
ANO5 LGMD2L)	7.4
SGCG (LGMD2C)	5.2
DNAJB6 (LGMD1D)	5.0
SGCA (LGMD2D)	4.8
GAA (Pompe)	4.7
MYOT (LGMD1A)	4.3
LMNA (LGMD1B)	4.1
DES (LGMD1E, 2R)	1.9
SGCB (LGMD2E)	1.1
CAV3 (LGMD1C)	0.9
Others (< 5 cases each)	
EMD (EDMD)	0.7
GNE (GNE myopathy)	0.7
ISPD (LGMD2U)	0.6
FKTN (LGMD2M)	0.2
TCAP (LGMD2G)	0.2
TRIM32 (LGMD2H)	0.2
TTN (LGMD2J)	0.2

(A, B) Results from more than 550 cases of limb-girdle muscle weakness that received a clearly definitive diagnosis from the MDA's panel of 35 genes. All cases were tested and analyzed by EGL Genetics (formerly the Emory Genetics Lab). Genes shown in blue indicate autosomal dominant cases of LGMD; autosomal recessive cases are shown in red. The desmin gene *(DES)* has been implicated in both a dominant and recessive form of LGMD (LGMD 1E and 2R, respectively) and thus is shown in purple. All genes shown individually were reported in at least five cases. "Others" refers to the seven genes which were reported in fewer than five cases; they are listed individually in panel B. No cases were reported for 11 genes: *TPNO3* (LGMD1F), *SGCD* (LGMD2F), *POMT1* (LGMD2K), *POMT2* (LGMD2N), *POMGnT1* (LGMD2O), *DAG1* (LGMD2P), *PLEC1* (LGMD2Q), *SYNE1* (EDMD), *FHL1* (EDMD), *SMCHDI* (Facioscapulohumeral dystrophy), and *VCP* (Inclusion body myositis).

from dedicated foundations, patient advocacy groups, and social media resources.

In addition to the benefits afforded to people living with disease, genetic testing positively impacts research and clinical development by the larger neuromuscular scientific community. Data are used to better understand disease epidemiology, characteristics, and pathogenesis. These data help experts periodically re-evaluate and refine care standards, and achieve clinical trial readiness by identifying patient cohorts, outcome measures, and possible biomarkers.[2] These benefits greatly facilitate and encourage the design, recruitment, and execution of clinical trials for specific diseases and disease subtypes.

In 2014, the American Academy of Neurology and the American Association of Neuromuscular & Electrodiagnostic Medicine published recommendations for appropriate genetic testing to be paired with clinical evaluation of suspected muscular dystrophies.[1]

The guidelines were endorsed by key organizations, such as the American Academy of Physical Medicine and Rehabilitation, the Child Neurology Society, the Jain Foundation, and MDA.

Even if recommended, however, genetic testing for limb-girdle muscle weakness can be expensive, not always covered by insurance, and not readily available in clinics. The MDA network of more than 150 neuromuscular specialty clinics provides the ideal infrastructure for a genetic testing program and, with support from Sanofi Genzyme, there is no cost to the patient.

What Has the MDA Genetic Testing Program Accomplished?

The MDA gene panel consists of 35 genes that cause known LGMD subtypes or other diseases that can cause similar symptoms. The test panel has been widely adopted by the medical community. Nearly 3,000 people have been tested

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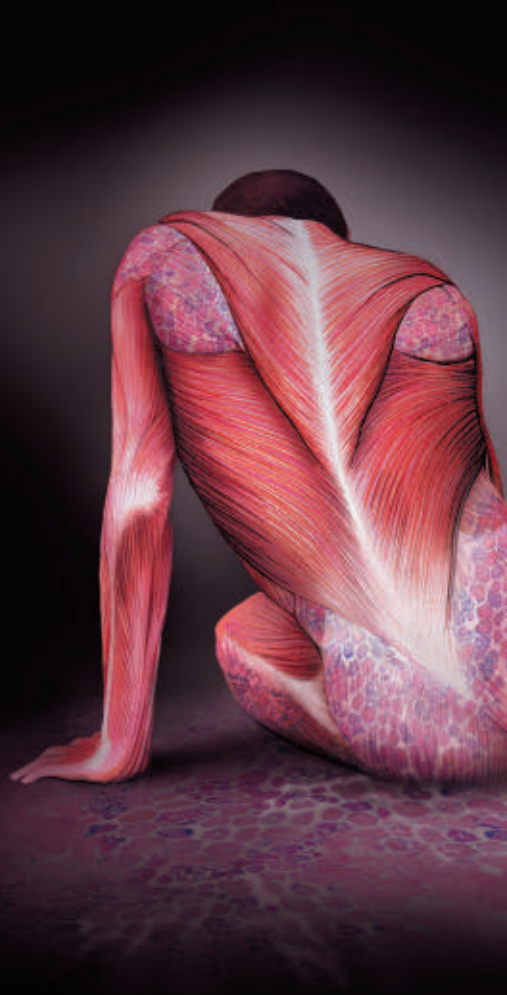
DISCOVER ADVANCED NEUROMUSCULAR TESTING

- Muscle biopsy
- Gene-panel testing[1]
- Various blood tests
- Electrocardiograms
- Nerve conduction tests
- Pulmonary function tests
- Reflex testing
- X-rays
- Magnetic resonance imaging
- Sleep studies
- Acid α-glucosidase assay



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Testing early can help impact a 13-year median diagnostic delay for Pompe disease.[2-4]

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Genetic Testing: MDA Paves the Way for Better Care in Limb-Girdle Muscle Weakness

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through the program since its launch in 2015, and its utilization is increasing.

In September 2017, MDA launched a LGMD awareness campaign that resulted in a significant uptick in requests for testing kits—more than 500 in the subsequent two months alone. This response highlights the importance of patient and provider education and awareness, and the continued need for affordable, accessible diagnostic options for people with limb-girdle muscle weakness.

Of nearly 3,000 people whose genetic profile was analyzed by testing so far, 27% received a diagnosis deemed clearly definitive (22% had two pathogenic recessive mutations or one pathogenic dominant mutation) or likely definitive (5% had one pathogenic recessive mutation and one variant of unknown significance [VOUS] in the same gene). Another 23% of cases were negative, in that no confirmed disease-causing mutation was found in any of the genes in the panel. The remaining 50% of cases were inconclusive VOUS, which would require further study to confirm whether they were the cause of disease. These findings are consistent with what has been reported by other neuromuscular disease genetic testing programs.[3,4]

Of the definitive diagnosis cases, subtype LGMD2A is the most frequent, reported more than twice as often as the next prevalent subtype, LGMD2B. The results for all definitive diagnosis cases are shown in the Figure. In general, autosomal recessive subtypes of LGMD (shown in red) are most prevalent, although significant cases of Bethlem myopathy, DMD, and late-onset Pompe disease have also been identified. Autosomal-dominant forms of LGMD (shown in blue) were identified in fewer cases—which is to be expected, given their relative rarity. Of all 35 genes on the panel, seven have been implicated in fewer than five cases, and 11 genes were not identified in any cases.

The impact of a diagnosis for the hundreds of people who have received one through the MDA genetic testing program cannot be overstated. However, there is still need and opportunity for the many people for whom the genetic cause of disease is still unknown. To this end, MDA funds research aimed at unveiling more of the biochemical significance of the VOUS, as well as funding new gene discovery in neuromuscular disease. Based on the results of those studies, new disease-causing genes and mutations can be added to the genetic testing panel.

In addition, in 2018, MDA plans to introduce new opportunities for people whose genetic testing was inconclusive. To achieve that goal, a new partnership between MDA and the Broad Institute at the Massachusetts Institute of Technology and Harvard University has been initiated to create a research program to pursue genetic diagnoses for a wider array of people served by MDA. As part of this program, people who were tested using the MDA gene panel and did not receive a definitive diagnosis will be able to receive more comprehensive genetic testing, including whole-genome sequencing, at no cost to them.

MDA's Multifaceted Goals

As understanding of the diverse causes of limb-girdle muscle weakness increases, and the diagnostic paradigm evolves, MDA will continue to expand its strategic offerings. Through collaborations with industry and academia, MDA's goals are to expedite diagnosis, optimize clinical care, and support new gene discovery, as well as to pave the path for expanded clinical development of dedicated therapies.

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Update on New Therapies and Testing for Rare Neuromuscular Diseases

The past year has been one of excitement and promise in the field of rare neuromuscular diseases. Major drug approvals for amyotrophic laterals sclerosis, Huntington's disease, and spinal muscular atrophy, among other disorders, are providing novel therapeutic options.

Jae Chang

The emergence of promising modes of therapy, such as gene therapy, coupled with the rapidly growing number of pharmaceutical companies entering the rare disease sector, has made the past year one of excitement and promise in the field of rare neuromuscular diseases. Major treatment approvals in amyotrophic lateral sclerosis (ALS), Huntington's disease, myasthenia gravis, and spinal muscular atrophy (SMA), among others, provide new therapeutic options for patients—some of them, the first of their kind. In addition, the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) released a consensus paper on the clinical usefulness of genetic testing in neuromuscular disease, reinforcing the important role genetic testing and patient registries play in the clinic and in patients' lives.

Amyotrophic Lateral Sclerosis

Edaravone. In May 2017, the FDA approved edaravone (trade name, Radicava; Mitsubishi Tanabe Pharma America) for the treatment of ALS, making it the first approved therapy for ALS in the US in more than 20 years. Before edaravone, the only FDA-approved treatment for ALS was riluzole, approved by the FDA in 1995. Riluzole is an antiexcitotoxic drug that targets overactivation of the principal excitatory neurotransmitter glutamate, which is hypothesized to lead to motor-neuron damage. Clinical trials of riluzole showed only mild and early increased survival of two to three months, however, without significant benefit to muscle strength or neurologic function.

Unlike riluzole, edaravone is a potent antioxidative agent believed to act as a free-radical scavenger, preventing the oxidative stress on neurons observed in ALS patients and thought to be a factor in the onset and progression of ALS. Edaravone was first approved in Japan in 2015 for the treatment of ALS; it was approved by the FDA in 2017 after the results of a randomized, controlled trial of 137 patients with ALS showed significantly less decline in motor function using the revised ALS functional rating scale (ALSFRS-R), especially when used concomitantly with riluzole early in the course of disease. Survivability with long-term use has yet to be determined.

Edaravone is an injection administered in cycles, initiated with intravenous infusion over 60 minutes every day for the first 14 days, then 14 days without infusion, with maintenance doses administered on 10 of the first 14 days of the next cycle, followed by another 14 days without infusion. According to Mitsubishi Tanabe, the price of one year of treatment will be $145,524; however, the manufacturer will offer copay or financial assistance, as well as free treatments for patients who qualify.

NurOwn and masitinib. Two treatments in the pipeline show potential as treatments for ALS. NurOwn, developed by BrainStorm Cell Therapeutics, is a mesenchymal stem-cell platform that can be engineered to secrete neuropathic factors to promote nerve-tissue growth and provide neuroprotection. The phase III study of NurOwn began patient enrollment late in 2017.

The same day that BrainStorm announced enrollment for its phase III trials of NurOwn, AB Science presented its phase III trial results for masitinib, a tyrosine kinase inhibitor

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Mr. Chang is a Doctor of Pharmacy candidate at Keck Graduate Institute School of Pharmacy, Claremont, California.

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that targets microglia, macrophage, and mast cell activity to inhibit the inflammatory processes seen in neurodegenerative disease. In the trial, patients received 48 weeks of treatment with either riluzole with placebo or riluzole with masitinib; results showed that patients receiving both riluzole and masitinib experienced slower decline in quality of life and significant delay in disease progression.

Huntington's Disease and Tardive Dyskinesia

Deutetrabenazine. In 2017, the FDA announced the approval of deutetrabenazine (brand name, Austedo; Teva Pharmaceuticals) for the treatment of chorea associated with Huntington's disease as well as tardive dyskinesia. Deutetrabenazine is the deuterated version of tetrabenazine, the only other drug approved for the treatment of chorea in Huntington's disease.

Notably, deutetrabenazine is the first deuterated drug, in which the so-called "heavy" isotope of hydrogen deuterium replaces hydrogen, giving it the same mechanism of action but a longer duration of metabolism. Deutetrabenazine and tetrabenazine appear identical at the vesicular monoamine transporter 2 (VMAT-2), where they reduce the availability of dopamine that is associated with motor symptoms in Huntington's disease and tardive dyskinesia. The stronger bonds of deutetrabenazine, however, allow for it to be given at a lower dosage, with lower risk of side effects, compared to its predecessor.

Results of phase III trials of deutetrabenazine showed significant reduction in chorea symptoms and better control over chorea symptoms, compared with tetrabenazine. The trial also showed that patients could safely switch from tetrabenazine to deutetrabenazine without loss of control over symptoms.

Valbenazine. The FDA also approved valbenazine (trade name, Ingrezza; Neurocrine Biosciences) in 2017 as the first treatment for tardive dyskinesia (before it was joined by deutetrabenazine later that year). Valbenazine is also a variant of tetrabenazine, the drug long-used for various movement disorders but associated with uneven response and the need for a high dosage or multiple doses.

Like its molecular cousins, valbenazine works at the VMAT-2 transporter to reduce the motor symptoms of tardive dyskinesia. The results of a phase III study of once-daily valbenazine showed a significant decrease in symptoms measured by the Abnormal Involuntary Movement Scale (AIMS) compared to placebo. The trial demonstrated that valbenazine produced significant improvement in tardive dyskinesia, while being well-tolerated and showing no evidence of decline in psychiatric status.

Ionis-HTTRx. A potential breakthrough drug, Ionis-HTTRx (Ionis Pharmaceuticals) successfully completed its first-in-human trials in 2017. The agent is an antisense oligonucleotide aimed at lowering the mutant protein huntingtin that is responsible for Huntington's disease. Ionis-HTTRx accomplishes this by stopping the mutated huntingtin gene from being translated into the problematic huntingtin protein. Results from phase I/IIa clinical trials showed dose-dependent reductions in huntingtin protein as well as a favorable safety and tolerability profile. Roche Pharmaceuticals licensed the investigational drug and initiated an open-label extension of the study, and plans to present results in the first half of this year.

> Major treatment approvals in amyotrophic lateral sclerosis, Huntington's disease, myasthenia gravis, and spinal muscular atrophy, among others, provide new therapeutic options for patients—some of them, the first of their kind.

Neuropathy

Immune Globulin Intravenous (Human), 10% Liquid. Late in 2017, CSL Behring announced that the FDA approved this compound (trade name, Privigen; CSL Behring) for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP), a rare autoimmune disorder in which the myelin sheath is attacked by the immune system, leading to peripheral nerve damage.

Approval follows the largest CIDP clinical study, PATH (Polyneuropathy And Treatment with Hizentra and another phase III study, Privigen Impact on Mobility and Autonomy (PRIMA). Results of PATH showed that 73% of patients receiving Immune Globulin Intravenous achieved response;

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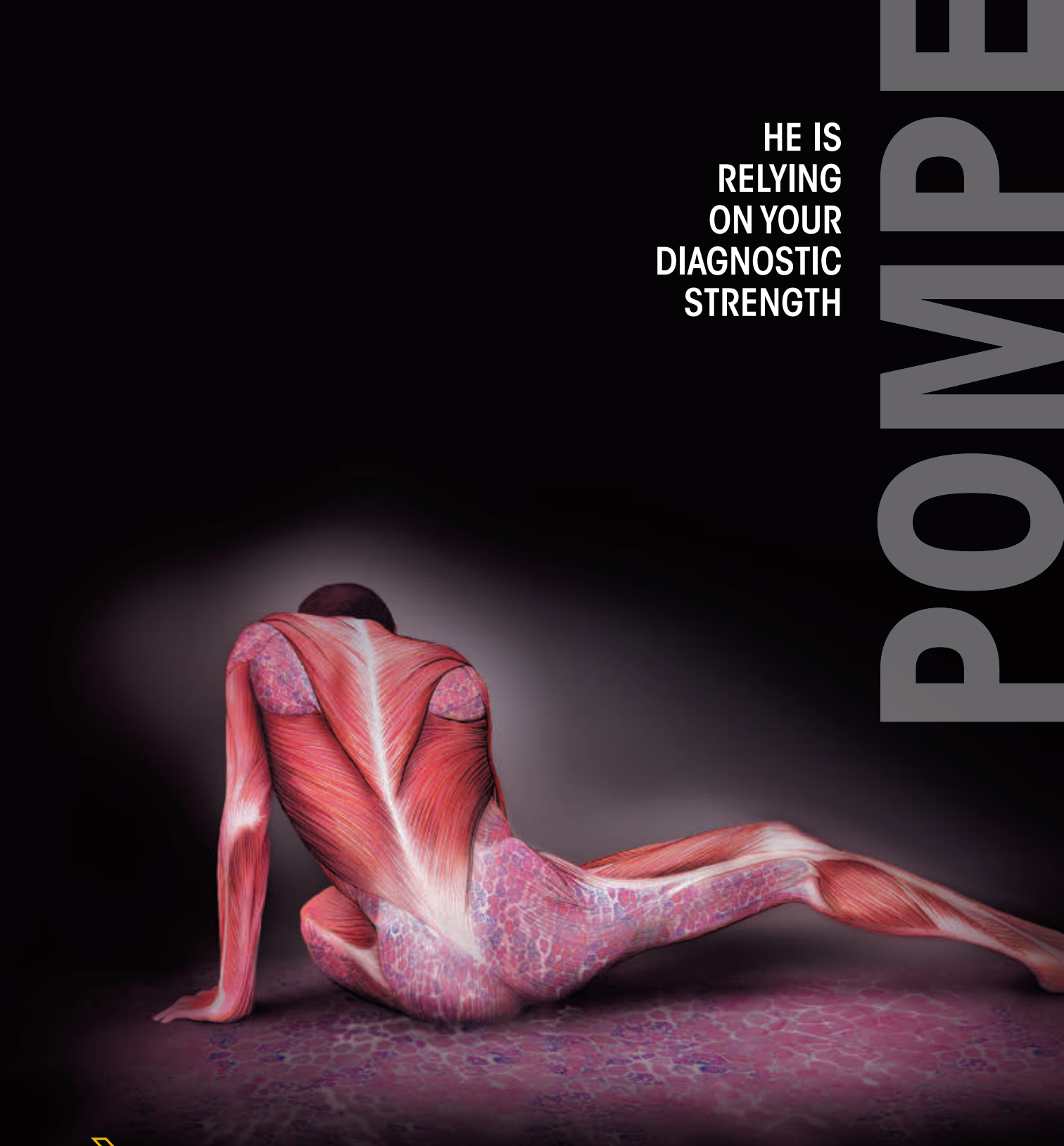

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Update on New Therapies and Testing for Rare Neuromuscular Diseases

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in PRIMA, the response rate was 61%. Approval of this agent for CIDP adds to its existing indications for primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura. Immune Globulin Intravenous adds another treatment option for patients with CIDP who did not respond well to other treatments.

Hizentra. The PATH trial also showed promising results for Hizentra, trade name of a subcutaneous form of Immune Globulin Intravenous (Human), 10% Liquid (Privigen). Patients with CIDP received Hizentra and were followed for 24 weeks of treatment. The results showed that Hizentra reduced the number of relapses and withdrawals compared with placebo; no patients withdrew because of adverse effects. Approval of Hizentra would mean a subcutaneous treatment option for patients with CIDP.

Myasthenia Gravis

Eculizumab. In October 2017, the FDA approved eculizumab (trade name, Soliris; Alexion) for the treatment of adult patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. This approval marks the first in more than 60 years for patients with myasthenia gravis. In the phase III REGAIN study and its open-label extension study, eculizumab demonstrated treatment benefits for patients with anti-acetylcholine receptor antibody positive generalized myasthenia gravis who had previously failed immunosuppressive treatment and continued to have significant unresolved disease symptoms, such as difficulty seeing, walking, talking, swallowing, and breathing. These patients, who represent approximately 5% to 10% of all patients with myasthenia gravis, are at increased risk of disease exacerbations and crises that may require hospitalization and intensive care and may be life threatening.

Spinal Muscular Atrophy

Nusinersen. 2016 ended with the arrival of nusinersen (trade name, Spinraza; Biogen), the first FDA-approved drug for SMA that also uses antisense technology as its mechanism of action. After successful results from the phase III CHERISH and ENDEAR trials, the enrolled pediatric patients with SMA were transitioned into the SHINE open-label trial, opening the study to patients with any type of SMA.

Continued data from trials showed significant improvements in survival and risk of ventilation assistance or death in patient receiving treatment with nusinersen. Data from patients with varying types of SMA continue to provide more evidence to push insurers to expand their coverage so that patients with all types (1-4) of SMA have access to the drug.

AVXS-101. In April 2017, biotechnology firm AveXis presented its findings from its first clinical trials of AVXS-101, a gene therapy for infants with SMA type 1. Data from a phase 1 trial of AVXS-101demonstrated significantly improved survival and motor skills. AXS-101 is undergoing a phase III trial (STR1VE) trial for infants with SMA type 1 and a phase I trial (STRONG) for children with SMA type 2.

SMA is caused by the mutated survival motor neuron *(SMN1)* gene, which leads to a decrease in SMN proteins that are necessary for maintaining the normal function of neurons. AVXS-101 uses the protein shell of a virus to carry and deliver a fully functional copy of the SMN gene into target motor-neuron cells, without altering the patient's DNA. The viral capsid protein AAV9 also carries the advantage of crossing the blood–brain barrier, allowing it to be administered intravenously.

The extended SMA pipeline. Drug development is focused on four strategies: *SMN1* gene replacement, SMN2-encoded protein modulation, neuroprotection, and targeted mprovements of muscle function:

Orally bioavailable agents for selective SMN2 splicing correction are entering clinical trials, after studies in mice showed increased SMN protein levels and motor function in preclinical studies.

Antisense oligonucleotides are also showing promise as Ionis-SMNRx (Ionis Pharmaceuticals) enters phase I open-label studies in patients with SMA types 2 and 3.

The neuroprotective agent olesoxime also concluded phase II trials, demonstrating that neuroprotective agents might have a place in the treatment of SMA.

Another strategy employs agents that improve neuromuscular function in SMA patients by varying methods, such as investigational agent CK-2127107 (Cytokinetics, Inc.) that aims to sensitize muscles and increase their contractile response to nerve signals.

Research continues to uncover new therapeutic targets. Hand in hand are more questions about how to better observe and measure the progression of SMA during clinical trials.

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AANEM
American Association of Neuromuscular & Electrodiagnostic Medicine

A community dedicated to improving the lives of patients with neuromuscular diseases.

Eric J. Sorenson, MD
AANEM President

Twenty years ago, Eric J. Sorenson, MD, joined the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM). His membership has had a significant impact on him both personally and professionally.

> "Very early in my career, one of my mentors encouraged me to join AANEM. He emphasized how it would make me a better electromyographer and offer me the opportunity to share my research while encouraging collaboration with others. AANEM's exceptional networking opportunities have given me the ability to engage with my peers from other medical centers and practices and expanded my perspectives on electrodiagnostic and neuromuscular issues."

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Update on New Therapies and Testing for Rare Neuromuscular Diseases

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Value and Utility of Genetic Testing

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) recently released a consensus paper regarding their position on the clinical usefulness of genetic testing in neuromuscular disease. The Association 1) provides a recommendation from experts in response to questions from clinicians and health insurance providers on the cost and benefits of testing and 2) outlines the reasons that those experts believe that genetic testing plays a vital role in the diagnosis, investigation, and monitoring of neuromuscular disease:

- **Better, more cost-effective care.** AANEM recognizes that diagnostic uncertainty may result in testing and treatments that may prove costly and unnecessary, while increasing the potential for the adverse events associated with them. Genetic testing aids clinicians in properly monitoring and managing patients, to avoid potentially treatable or avoidable comorbidities. AANEM provides the example of considering defibrillator-pacemaker implantation in a patient with limb-girdle muscular dystrophy type 1B—a type whose distinguishing characteristic is a high risk for ventricular arrhythmia. Testing can guide therapy and determine how patients should best be monitored.

The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) recently released a consensus paper regarding their position on the clinical usefulness of genetic testing in neuromuscular disease.

- **Reducing psychosocial impact by confirming a diagnosis.** For patients and their family, uncertainty has a significant impact on wellness; confirmation of a diagnosis might allow patients to find closure and seek resources based on that diagnosis.
- **Family planning.** The statement also points to how testing could help patients who are planning to have children to make informed decisions and be encouraged to undergo genetic counseling.

Genetic testing may become essential for patients who want to participate in a clinical trial. Given the number of new and varying modes of treatments being investigated, a molecular diagnosis may, in fact, be required for participation. A molecular diagnosis also allows patients to be included in such vital resources as a patient registry or a biobank. Access to these resources may be invaluable to researchers and patients, thus justifying the cost of genetic testing.

SUGGESTED READING

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Peripheral Neuropathy: Navigating Diagnosis and Treatment

Peripheral neuropathy is a broad term for a condition that can be motor or autonomic, inherited or spontaneous, primary or secondary, common or rare. But in all cases early diagnosis and appropriate treatment can improve outcomes.

Treatment of peripheral neuropathy, a condition that affects as many as 20 million people in the US, hinges in part on treating the underlying cause of nerve damage. "For about 30% of patients, however, there is no known reason for neuropathic pain, which makes treatment challenging," said Jafar Kafaie, MD, PhD, Assistant Professor of Neuromuscular Diseases at Saint Louis University School of Medicine.

"Small fiber neuropathy predominantly affects the peripheral nervous system, which detects sensations such as temperature and pain," Dr. Kafaie said. "For many patients, there can be mixed neuropathy, which involves the motor and autonomic nerves as well as the sensory nerves." Patients with motor neuropathy experience muscle weakness and those with autonomic neuropathy have symptoms that may include urinary and digestion problems, sluggish pupil reaction, and sexual dysfunction.

Early diagnosis and prompt initiation of treatment can improve disease outcome; however, patients who have pain for more than six months can develop chronic pain syndrome. "At that point, supportive therapies and pain management become important," Dr. Kafaie noted. "Comprehensive clinics involve psychiatrists as well as pain specialists to treat painful neuropathy." Dr. Kafaie presented his overview at the Hereditary Neuropathy Foundation's Patient-Centered Charcot-Marie-Tooth/Hereditary Neuropathy Pressure Palsies Pain Summit.

Causes and Diagnosis

In addition to idiopathic disease, peripheral neuropathy can arise from genetic or secondary causes, Dr. Kafaie said. Genetic mutations can either be inherited or spontaneous. While some genetic mutations lead to mild neuropathies with symptoms that begin in early adulthood and result in minimal impairment, more severe hereditary neuropathies often appear in infancy or childhood. The most common of the hereditary disorders to cause motor and sensory neuropathy is Charcot-Marie-Tooth disease, affecting approximated 1 in 2,500 people. Charcot-Marie-Tooth disease is characterized by progressive loss of muscle tissue and touch sensation across various parts of the body.

"For peripheral neuropathy of nongenetic causes, the symptoms are highly variable," Dr. Kafaie said. "They usually include burning pain, stabbing pain, or shooting pain that starts in the toes, progresses upward to the legs, and eventually affects the fingertips. When the nerve dies, the pain is replaced by numbness."

Performing a thorough neurological examination and taking an extensive medical history is required to determine the cause of the symptoms, Dr. Kafaie noted. Secondary causes of painful neuropathy include the following:

- Physical trauma (e.g., automobile accidents, falls, sports-related activities) and repetitive stress
- Metabolic and endocrine disorders, most notably diabetes mellitus
- Autoimmune diseases, such as Sjögren's syndrome, lupus, rheumatoid arthritis, and Guillain- Barré syndrome
- Kidney disorders
- Cancer/tumors
- Viruses and bacteria that can attack nerve tissues, such as herpes varicella zoster, Epstein-Barr, herpes simplex, Lyme disease, and diphtheria
- Environmental or industrial toxins, such as lead, mercury, and arsenic
- Chronic alcohol consumption, which in turn can lead to vitamin B12, thiamine, and folate deficiency.

Diagnosis

Based on the results of the neurological examination and patient history, additional tests may be ordered to help determine the nature and extent of the neuropathy, Dr. Kafaie said. Nerve conduction velocity (NCV) tests

measure the degree and type of damage in large nerve fibers. During this test, a probe electrically stimulates a nerve fiber, which responds by generating its own electrical impulse. An electrode placed further along the nerve's pathway measures the speed of impulse transmission along the axon. Slow transmission rates and impulse blockage tend to indicate damage to the myelin sheath, while a reduction in the strength of impulses at normal speeds is a sign of axonal degeneration.

Skin biopsy is a simple procedure during which doctors remove a thin skin sample from the upper or lower extremity and examine the nerve fiber endings under a microscope. Unlike NCV tests, skin biopsy can reveal damage present in smaller fibers, which are unmyelinated, Dr. Kafaie said. It also is less invasive than conventional nerve biopsy, which involves removing and examining a sample of nerve tissue, most often from the lower leg. "Skin biopsy is easier to perform than nerve biopsy, and nerve biopsy itself may cause neuropathic adverse effects."

Electromyography can detect abnormal electrical activity in motor neuropathy to help differentiate between muscle and nerve disorders. MRI can show muscle quality and size, detect fatty replacement of muscle tissue, and help rule out tumors, herniated discs, or other abnormalities that may be causing the neuropathy.

Treatment

The first step in treating peripheral neuropathy is to address any contributing causes, such as glucose control, infection, or vitamin deficiency. "Peripheral nerves have the ability to regenerate axons, which can lead to functional recovery," Dr. Kafaie said. "But once the nerve cell has died, the damage is irreversible. The goal then becomes to manage symptoms." Mild pain can sometimes be alleviated by over-the-counter analgesics such as NSAIDs. Other common treatment options include antidepressants, anticonvulsives, topical agents, and opioids.

Antidepressant and anticonvulsant medications have been shown to modulate pain through their mechanism of action on the peripheral nerves, spinal cord, or brain. In a Cochrane review of studies, tricyclic antidepressants in particular were found to confer at least moderate relief of neuropathic pain, Dr. Kafaie pointed out. In 2004, duloxetine hydrochloride, a serotonin and norepinephrine reuptake inhibitor, was approved by the FDA to treat pain caused by diabetic peripheral neuropathy. Anticonvulsant medications frequently prescribed for neuropathy include gabapentin, pregabalin, topiramate, and carbamazepine. "Duloxetine and gabapentine are often prescribed together for their synergistic effects, as duloxetine appears to soothe the irritated peripheral nerves and gabapentine works at the spinal cord," said Dr. Kafaie.

Topical medications such as lidocaine and capsaicin are another option for neuropathic pain. For pain that does not respond to the previously described medications, the addition of narcotic agents may be considered. However, their use should be a last resort as it can lead to dependence and addiction, Dr. Kafaie said. Tapentadol, a drug with both opioid activity and norepinephrine-reuptake inhibition activity, was approved to treat diabetic neuropathy in 2012.

"Another important treatment modality is cognitive behavioral therapy," Dr. Kafaie said. "It doesn't take the pain away but teaches the patient effective ways to deal with the pain. It also helps with the depression." Unlike psychoanalysis, cognitive behavioral therapy does not deal primarily with the past but rather focuses on current problems and finding solutions for them.

"There also are various nerve stimulation devices on the market, but none of them have enough scientific data to support their use," he added.

—Adriene Marshall

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‘Hunting’ for Workable Methods of Gene Therapy

There is the promise of good outcomes from gene therapy in Huntington’s disease because the monogenetic inheritance characteristics of the disorder make it an ideal candidate for treatments that target DNA and RNA.

Caroline Kim and Ronald J. DeBellis, PharmD

Gene therapy has recently emerged as a new therapeutic option, when indicated. Through research, gene therapy has progressed from a dream in the late 1970s to an FDA-approved, clinically effective therapy in the 21st century. Some genetically-oriented diseases devoid of treatment 40 years ago can now be treated with gene therapy.

Gene therapy has various methods of delivery that use genes to treat or prevent diseases by replacing a mutated gene with a desired therapeutic copy of the gene. It inactivates, or “knocks out,” a mutated gene that is functioning improperly and introduces a new gene into the body to help fight disease.

The promise and understanding of delivering gene therapy, after years of research targeted to designing mechanisms by which to deliver genes, has come into being. Huntington’s disease is one of the genetically-oriented diseases for which gene therapy promises good outcomes because the monogenetic inheritance characteristics of Huntington’s disease make it an ideal candidate.

‘Bright’ Outlook for Gene Therapy in Huntington’s Disease

With roughly 30,000 people in the United States having a diagnosis of Huntington’s disease, it is categorized as a rare disorder with a specific genetic origin. Patients with Huntington’s disease have abnormalities of both physical and neurological function, such as personality changes, impaired judgment, involuntary movements, memory loss, and slurred speech. The nature of Huntington’s disease is a progressive course, and only limited treatment options are available to mitigate symptoms.[1]

The outlook for gene therapy in Huntington’s disease is bright because of the disease’s unique mutation in the targeted *HTT* gene. The *HTT* gene is necessary to provide instructions for making a protein, huntingtin; the essential role of huntingtin is incompletely understood, but it is thought to have a pivotal role in the development in the nerve cells of the brain through vesicular transport of nutrients.[2]

In Huntington’s disease, the huntingtin protein is ubiquitously overexpressed by the mutated *HTT* gene.[3] The mutation occurs with an expansion of the CAG (codon) trinucleotide repeat in the *HTT* gene at a level four-fold above normal. The increased repeat of the CAG segment abnormally elongates the huntingtin protein, which, essentially, is cut into smaller fragments and binds irregularly together, to cause toxic gains of function.[4] In addition, HTT messenger RNA (mRNA) has been shown to affect the repeat associated non-ATG (RAN) translation that can generate irregular protein fragments from both sense and antisense strands of genetic material, which can also lead to toxic functionality.[5]

This is an opportune time for gene therapy to target treatment of neurodegenerative disease: Several antisense oligonucleotides (ASOs) are being studied in model systems. The first targeted HTT-lowering compound has been cleared

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'Hunting' for Workable Methods of Gene Therapy

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to enter human trials: the synthetic 20-nucleotide sequence IONIS-HTTRx (Ionis Pharmaceuticals and Roche), which targets human HTT and is designed to reduce production of the HTT protein by disabling the mRNA responsible for producing huntingtin protein through action on the antisense strand, thereby preventing creation of the damaged proteins.

The Phase I/IIa clinical trial of IONIS-HTTRx is primarily focused on the safety of the drug by slowly increasing the dosage of the agent in comparison to placebo, with careful monitoring. In addition to safety, the study examines aspects of the pharmacokinetics of IONIS-HTTRx in the human central nervous system that will engage biomarkers, including mutant HTT in cerebrospinal fluid. IONIS-HTTRx as an antisense drug that lowers huntingtin production appears to be a promising therapeutic strategy to prevent or slow the progression of Huntington's disease.[6-8]

Few other specific ASO therapies that target downgrade of the mutated *HTT* gene were under investigation in 2017.[9] One investigational therapy targeted single nucleotide polymorphisms containing regions of HTT mRNA, which work as a selective silencing of the mutant allele. Another investigation focused on targeting the CAG repeat of mutant *HTT* that also selectively silenced that mutant allele.[10]

Gene-Editing Therapies

DNA-targeting therapeutic agents are making their entrance as gene-editing treatments. Gene-editing technology exerts permanent and elaborate proofreading effects at the genome level, thus representing a key development in gene therapy. This concept is apt to raise ethical issues, but DNA editing in fact targets the germline so that the disease will not affect future offspring.[11]

Under study for Huntington's disease in various animal models are two DNA-targeting gene therapies: zinc finger proteins and CRISPR-Cas9. Both use protein-coding sequences encapsulated by a viral vector, which is injected intracranially to spur transduction of host cells, prompting them to produce a functional, non-native therapeutic protein.[12]

- **Zinc finger proteins** are synthetically generated to target a specific DNA sequence of interest. The zinc finger array is designed to contain one finger for every three bases of DNA that are fused to a function domain on the DNA. The array can cleave the DNA, at which point zinc finger transcription factors are able to modulate gene expression.[12]

Because the zinc finger protein process may lack precision for therapeutic application in post-mitotic brain cells of a patient with Huntington's disease, the use of zinc finger proteins has been studied to be more specific in targeting the CAG-repeat stretches that are closer to the 3'end in the *HTT* gene. The study, being conducted in animal models, has been successful in reducing mutant HTT protein expression without affecting other, non-mutant HTT proteins. The hope is that this approach can reduce the production of non-native proteins that can trigger inflammatory and immune reactions that can cause neuronal death. Ultimately, the process would target a decrease in the mutant HTT rebound rate and suppress mutant HTT over the long term for all carriers of the mutation.[12,13]

- **CRISPR/Cas9 technology** opens possibilities of excision of CAG repeats in Huntington's disease to form nontoxic alleles that are capable of inactivating the mutant HTT allele by insertion of stop codons or missense mutations.[14] The goal of this excision is permanent removal of the abnormal sequence in both RNA and the mutant HTT protein. The method was tested successfully in 2017 in a rodent model, with selective reduction in the mutant HTT allele and improved motor function—but no improvement in survival. The investigation anticipates broadening model systems to enhance vector delivery methods and target immunogenic bacterial proteins associated with the therapy.[15,16]

Progress Is Encouraging

Huntington's disease is particularly appropriate for gene therapy that targets DNA and RNA to modulate protein expression. Molecular therapies have demonstrated accelerating progress for this neurologic disease, and researchers are looking ahead in anticipation that scientific advancement will bring promising novel trials that show improvements in the delivery and distribution of genetic treatments via the central nervous system.

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Needed: A 'Rare' Distinction of Care in Specialty Pharmacy

Standardization and accreditation in pharmacy care that combines technology and conversation might help alleviate obstacles of access, drive advocacy, and improve outcomes in rare-disease management—and allow pharmacies to be reimbursed for providing premium care.


Ronald J. DeBellis, PharmD, and Micaila Ruiz, PharmD, RPh

Specialty pharmacies, and the medications they dispense, do not represent a new kind of pharmacy practice; they have been around for many years. Only recently, however, has the spotlight begun to intensify around this area.

There is no standardized definition of what classifies a drug as a "specialty medication," although a few of the criteria used are high price, use in chronic illness requiring more touchpoints with patients, and special need for storage and distribution.[1] Orphan drugs are routinely lumped into the broad category of specialty drugs, and are not recognized as existing for a specialized population of patients who face frustratingly complicated diagnostic and therapeutic hurdles (that is, when therapy is available).

In fact, conversations involving purchasing, dispensing, and business models seemingly revolve around specialty drugs in specialty pharmacies and never differentiate between specialty and orphan drugs, even though there is clear distinction between the two.[2-5] The Orphan Drug Act of 1983 designates drugs for orphan status if:

- the disease for which the drug is used affects fewer than 200,000 people in the United States.
- the disease for which the drug is used does affect more than 200,000 people in the United States, but there is no reasonable expectation that the cost of developing the drug and making it available in the United States to treat the disease will be recovered from sales in the United States.[6]

The elusive definition behind specialty drugs does not do anything to deter intense public scrutiny around skyrocketing prices. Many articles have been written regarding drug pricing in which specialty and orphan drugs are lumped together. A 2017 Quintiles/IMS (now IQVIA) report,[7] funded by the National Organization for Rare Disorders (NORD), delineates drugs by definition as "all medicines," "specialty medicines," "traditional medicines," and "orphan drugs." These distinctions recognize that orphan drugs as a unique category of medications, warranting their own standards by which to be measured.

A clear definition of what is, and is not, considered a specialty medication has produced a number of challenges, especially for patients who have a rare or orphan condition. In this article, we attempt to clearly distinguish the rare and orphan population, and the limited number of medications used to treat these conditions, from the generalized specialty pharmacy category. We also highlight the need to define standards of care for patients who have a rare or orphan diagnosis. No accreditation standards exist for specialty pharmacies that directly address the needs of the rare disease population. This lack of standardization of care for patients who have a rare or orphan disease creates a myriad of additional problems for patients who already face innumerable obstacles to receiving appropriate care.

In the same Quintiles/IMS Institute report, the specialty drug market was defined as comprising two categories: specialty non-orphan drugs and specialty orphan drugs.[7] This

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distinction is significant—not only from the perspective of drug sales but also from the standpoint of care. Specialty pharmacy accreditation exists largely to address the specialty non-orphan drug aspect, as this constitutes more than 80% of the specialty drug market—leaving the orphans and rare disease population without specific metrics about pharmacy care.

Regarding Patient Care

The practice of pharmacy has advanced clinically as a profession through the advent of evidence-based medicine and documentation of clinical intervention services on the premise that, if it cannot be measured, it cannot be done. There are marketing claims that specialty pharmacies care for the rare disease patient population, but the metrics are absent that specifically measure pharmacy care outcomes in the rare disease population.[8,9]

Effective drug therapy is considered by the rare disease community to be the ultimate milestone during the patient journey. There are few cures in this space, although a therapy that reduces the burden of disease, improves quality of life, or simply provides hope is a significant outcome. Being able to measure the quality of care, pharmacy–patient–family partnerships, successes, and failures on the journey with an orphan medication would be significant in the care of patients with rare diseases.

But few therapies for these patients ever reach market. Out of nearly 5,800 drugs that received orphan status designation, roughly 450 have been approved.[10] For drugs that receive FDA approval based on clinical trials that enrolled a low numbers of patients—such as Sarepta Therapeutics's eteplirsen (trade name, Exondys 51) for Duchenne muscular dystrophy—specialty pharmacies are in a unique position to capture data during the additional two-year period allowed in this instance, during which additional data are to be provided to the FDA to supplement original clinical trial data that was presented to the FDA for approval.[11]

Accrediting Pharmacists, or Pharmacies, in Rare Disease Care?

Creating accreditation standards applicable to individual pharmacy locations where there is a nidus of patients with rare diseases may be one way to achieve a designated, measurable pharmaceutical care path for the patient with a rare disease. Developing accreditation standards and recognizing pharmacies as NORD-designated centers of rare disease pharmaceutical care would be beneficial in the rare disease space—as opposed to providing rare disease certification for pharmacists, as is done in such specialties as oncology. There are simply too many rare diseases, and not enough time dedicated in the professional education process (due to core accreditation standards), for a pharmacist to become a rare disease specialist.

We believe that standardizing the approach to pharmacy care in the rare disease population would be well received by patients, their families, and their providers. Focusing on accreditation of specialty pharmacies ensures that the core needs of *all* patients who have a rare or orphan condition are met through pharmacy-specific standards of accreditation.

With respect to providing a designation in rare diseases to pharmacies, versus certification of pharmacists, consider the situation in oncology. Every pediatric oncology patient is considered, by definition, to have a rare disease. The breadth of knowledge required in this specialty is immense (and oncology is just one aspect of the rare disease space!). How can we expect health professionals, of any profession, to master information pertaining to all 7,000-plus rare diseases? (See "Did You Know? Rare Disease Statistics"[12])

There may be a way, in the future, to designate rare diseases as a specialty in pharmacy: namely, through a medical genetics specialty that will likely evolve from current research and focus on genetic therapy. For now, designating individual pharmacies, as opposed to individual pharmacists, seems to be a more streamlined and implementable approach that would appeal to specialty pharmacies.

Did You Know? Rare-Disease Statistics[12]

- A rare disease is defined as one that affects one of every 200,000 people
- Approximately 7,000 rare diseases have been identified
- Rare diseases affect 25 to 30 million Americans
- Some rare diseases affect only a few hundred, or even just a few dozen, people
- Rare diseases are usually serious or life threatening
- More than 80% of rare diseases have a genetic origin
- Fifty percent of rare disease patients are children
- Treatments for rare diseases usually address symptoms; few, if any, are a cure
- On average, a person with a rare disease visits 7.3 different physicians before receiving a diagnosis
- On average, a person with a rare disease has symptoms 4.8 years (range, 3 to 9 years) before receiving a diagnosis
- Patient with a rare disease find that the number of medical experts who have knowledge of their disease is limited
- All patients with a rare disease experience financial burden, inability to attend school or work, and social isolation

As scientific advancement continues to outpace the US health care economic infrastructure, and as more advanced therapies enter the market, there is a growing need for this type of recognition to serve the rare disease community. The designation we describe makes it possible to provide high-level pharmacy care to patients with rare diseases—who, often, have few health care options and access to seemingly fewer health care workers who understand a given patient's rare disease.[13]

In addition to advances in the treatment of rare diseases, there will be a new level of understanding required about payment models (e.g., value-based therapy) for those therapies—the burden of which will likely fall on specialized, rare disease pharmacies, to some degree.[14] In this article, we are proposing shifting (much like the way the profession of pharmacy generally is changing), the focus away from drug *product* and developing an argument to advance pharmaceutical care for patients with rare diseases so that it addresses their *comprehensive care*.

Medication, Metrics, and Money

Let's shift back to the product and consider metrics to optimize product use—metrics that generate data reflecting real-time and real-world outcomes that are standardized and comparable across institutions. Because payment models have yet to keep pace with scientific advancement, every touchpoint on the spectrum of care will need to demonstrate *value*. Today, specialty pharmacies use standards of best-practice operations that are provided by one or more accrediting bodies. The next step? To home in on items that are specific to the rare disease population and transform those standards to metrics that provide data on quality of care in the rare disease patient.

As reimbursement in the health care system migrates from fee-for-service to pay-for-performance, pharmacies will need to adapt. Through the Centers for Medicare and Medicaid Services's Five-Star Quality Rating System, pharmacies have an effect on Medicare Part D measures. Management of chronic conditions has been demonstrated to effect Five-Star ratings—through adherence, medication safety, and medication therapy management.[15]

In addition to vigilance paid to accreditation and technology tracking, discussions need to occur among specialty pharmacies that have a rare disease designation, the pharmaceutical industry, relevant patient organizations, and the FDA to identify value surrounding products that are in clinical trials and appear to be ready for approval and marketing.[16] This multi-stakeholder interaction should lay the groundwork for a rare disease-designated specialty pharmacy platform.

A platform of standardization will set a new norm in caring for patients with rare diseases, and will help acknowledge that this population is in need of recognition. The combination of technology and conversation might help alleviate issues with access, drive advocacy, improve outcomes—and allow pharmacies to receive reimbursement for providing premium care.

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CADASIL: The Migraine–Stroke–Dementia Connection

Three disabling neurological conditions converge in the most common monogenic cerebral small-vessel disease, making management both a supportive and a preventive undertaking.

Karen D. Orjuela, MD

In 1993, at the Lariboisière Hospital in Paris, Professor Marie-Germaine Bousser, in collaboration with Professor Elisabeth Tournier-Lasserve from the French National Institute for Health and Medical Research (Inserm), mapped chromosome 19 in 57 members of a family suffering of an unusual presentation of cerebral small-vessel disease, migraine, and cognitive decline. The powerful academic interest of Professor Bousser and her team led the subsequent identification of a mutation of the *Notch3* gene responsible for the disease in that family—a landmark discovery in the understanding of monogenic diseases in vascular neurology.[1,2]

The name assigned to this condition is CADASIL (***C***erebral ***A***utosomal ***D***ominant ***A***rteriopathy with ***S***ubcortical ***I***nfarcts and ***L***eukoencephalopathy). Since its discovery, the *Notch3* gene mutation has been identified in many families worldwide. The estimated prevalence is two to five cases for every 100,000 people.[3]

The *Notch3* gene is located on chromosome 19p13 and encodes a transmembrane receptor expressed in smooth muscle and pericytes. The receptor has a large extracellular domain, with 34 epidermal growth factor-like repeats (EGFRs) encoded by exons 2-24—the site at which CADASIL mutations are most often found. The *Notch3* gene also has a transmembrane and an intracellular domain. Each EGFR has six cysteine domains that form disulfide bonds, contributing to the protein's tertiary structure. Approximately 200 *Notch3* gene mutations have been associated with CADASIL; most are stereotyped missense substitutions of one base that cause loss or gain of cysteine residue in one of the EGFRs.[3,4]

Presentation, Diagnosis, and Counseling

Although some physicians are not familiar with CADASIL, we all know that listening to the patient is never a bad idea, especially if there is family history of migraine, early lacunar strokes, and dementia in close relatives. CADASIL presents in an autosomal-dominant fashion, involving predominantly the cerebral small vessels, with distinct findings on brain magnetic resonance imaging (MRI) T2-weighted and fluid-attenuated inversion recovery, or FLAIR, sequences. CADASIL diffusely affects white matter, but prominently the external capsules and anterior poles of the temporal lobes and superior frontal gyri, displaying a characteristic pattern of leukoencephalopathy[2,3] (Figure).

Migraine with aura is usually the first symptom of CADASIL, presenting early in adulthood, although variations among different populations and races have been reported; the incidence of recurrent ischemic stroke, psychiatric disturbances (such as apathy), and subsequent dementia seem to increase during the fourth decade of life.[2,3] A CADASIL scale serves as a pre-genetic analysis screening tool that helps identify patients with clinical and radiological findings and a family history of CADASIL, in anticipation of *Notch3* gene testing.[5]

CADASIL affects smooth-muscle cells of small arteries and arterioles, with subsequent loss of muscle cells that induces fibrosis and vessel-wall thickening. Granular osmiophilic material (GOM) deposits accumulate in the basal membrane close to the endothelium and the mutant Notch3 protein accumulates in the media. Other cell types are affected, too, including pericytes and endothelial cells of the brain. GOM deposits can also be found in small vessels of peripheral nerves, skin, and muscle.[6]

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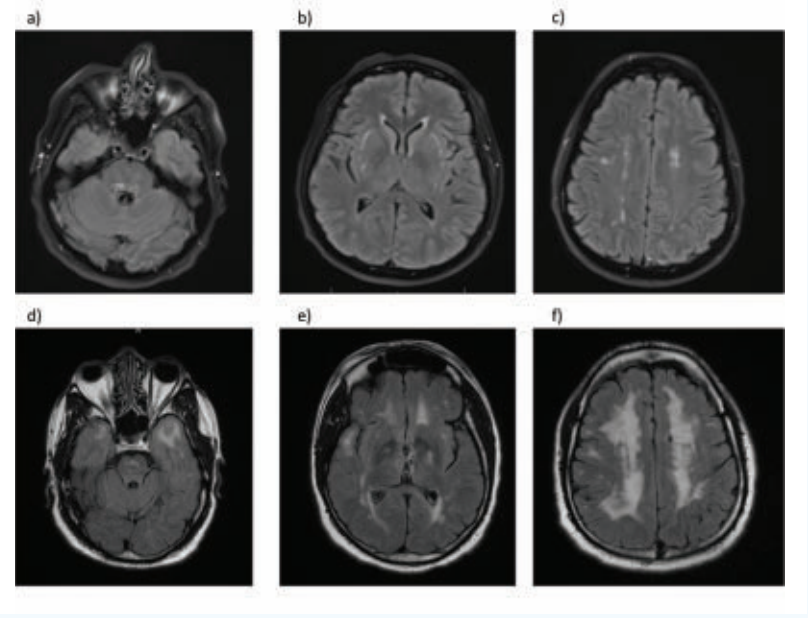
FIGURE: Axial T2 FLAIR MRI of the brain



Axial T2 FLAIR MRI of the brain showing multiple subcordial white matter lesions, involving the pons (**a**) external capsules (**b**), bilateral temporal poles (**d,e**) and periventricular and frontaoparietal regions (**c,e,f**).

Genetic counseling should be offered to all patients with CADASIL and undertaken before predictive genetic testing, using Huntington's disease guidelines.[7,8] Confirming the diagnosis of CADASIL requires screening for the 23 exons encoding the 34 EGFRs and evidence of a *Notch3* gene mutation; this test has nearly 100% specificity and sensitivity. Skin biopsy (specificity, 100%; sensitivity, 45% to 100%) reveals mutant Notch3 protein in the vessel wall; electron microscopy reveals GOM in vascular smooth-muscle cells.[2,3]

Other ancillary tests are useful to exclude other potential diseases, including blood tests, electromyography, cerebrospinal fluid analysis, and MRI of the spinal cord. CADASIL can be misdiagnosed as multiple sclerosis, as described in some case reports and series, although the presence of characteristic CADASIL neuroimaging findings and genetic testing helps avoid such a mistake.[9] Cardiovascular studies, including electrocardiography and echocardiography, are usually unremarkable, although findings from a series of cases from Italy suggests an elevated incidence of right-to-left shunt in these patients.[10] Large-vessel artery involvement has been also reported in a study of cerebral catheter angiography[11]; however, cerebral catheter angiography should be avoided because of the risk of complications that it presents.[12]

Treatment

There is no definitive treatment for CADASIL, but close monitoring and control of cardiovascular risk factors is advised. Therapeutic strategies for managing acute migraine attacks are analgesics, such as acetaminophen and antiemetics, and, in earlier reports, sodium valproate. Triptans and ergot derivatives could cause additional endothelial damage because of their vasoconstrictive properties.

CADASIL patients presenting with a suspected vascular syndrome that suggests acute stroke should receive intravenous thrombolytic therapy with tissue plasminogen activator, absent contraindication. A potential increase in the risk of intracranial hemorrhage from thrombolytic therapy, due to the presence of previous microbleeds, has been hypothesized, but successful and uncomplicated courses of thrombolytic therapy in these patients have also been reported.

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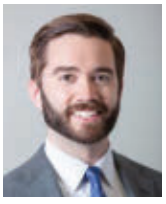
NORD's Federal Policy Outlook, 2018

The top priorities on NORD's federal policy advocacy agenda are elucidated by the organization's Director of Federal Policy.



Paul Melmeyer

At the 2017 National Organization for Rare Disorders (NORD) Rare Disease and Orphan Products Breakthrough Summit in Washington, DC, Paul Melmeyer, NORD's Director of Federal Policy, summarized the top priorities of NORD's federal policy advocacy agenda for 2018. "Perhaps we should frame it all in an optimistic light and say these are all opportunities that we will face in 2018," he said. Now over a month into 2018, many of the priorities remain the same, but many have been shifted by the enacted tax reform, Trump Administration activities, and the special election in Alabama.

Orphan Drug Act

"First and foremost is protecting the Orphan Drug Act," he said. "There's still a lot of misinformation out there on what the Orphan Drug Act does and does not do, what it allows and what it does not allow. NORD is concerned that this misinformation could be turned into policy initiatives designed to address problems that may not exist. NORD believes this is going to be one of the most important roles we will be playing in 2018. An important priority is defending the incentives of the Orphan Drug Act, which have led to more than 600 orphan indications over the prior 35 years," he said. While much has changed since NORD's October summit, protecting the Orphan Drug Act still remains their top priority for 2018.

Patient Protections, Medicaid, and the Affordable Care Act

Another federal priority is defending insurance patient protections and Medicaid coverage. "This is a fight that NORD has been fighting in 2017 and it is certainly not going away," Mr. Melmeyer said. "What we saw in the last quarter of 2017 was one executive order and one additional announcement from the White House. There was the announcement that there would be a two-part rollback of certain provisions within the Affordable Care Act, the first being the allowance for association plans, which are much more loosely regulated. This would lead to key patient protections being jeopardized. These association plans do not need to comply with some of the protections that were in the Affordable Care Act, such as community rating protections and other protections around benefit exclusions and guaranteed issuance," Mr. Melmeyer said. Association plans would allow those who are healthier to segment themselves off into a separate risk pool, leaving patients who need more comprehensive care, and would not qualify for an association plan, left within the marketplaces, thus driving up their premiums and potentially costing them access to insurance altogether. "We also saw within the executive order an expansion of the allowance for short-term plans," Mr. Melmeyer said. Under the Affordable Care Act, short-term plans could only be acceptable for three months; under the new executive order, that would be extended to one year. "Again, these short-term plans do not have to comply with patient protections," he said.

Sure enough, the Administration has since moved forward with their Association Health Plan proposal, and is still exploring their short-term plan proposal. In addition to the Administration's activities, Congress also successfully repealed the individual mandate as part of tax reform, further undermining the stability of the Affordable Care Act.

While all of these moves are concerning, the unsuccessful attempts to fully repeal the ACA, coupled with the changing makeup of the Senate, make it very unlikely Republicans will be able to go further legislatively this year than they've already gone.

Medicaid federal assistance is also in jeopardy. "We've seen several bills that have proposed cutting Medicaid by upwards of $800 billion within the next 10 years. We do not imagine that Medicaid is by any means safe. We see activity in the states with 1115 waivers in which states have requested that the federal government allow them to loosen their regulations and limit the amount of what they will have to cover in their states. And we imagine that federal funding to the states could be drastically reduced."

While Congress has been unable to legislate cuts to the Medicaid program, and will probably continue to be unable to do so through 2018, the states have increased their requests for 1115 waivers to change their programs and institute work requirements. This will be one of NORD's main state and Federal priorities for 2018 to ensure rare disease patients and their families keep their Medicaid coverage.

Stabilizing the Health Insurance Marketplace

"Aside from defending patient protections and Medicaid access for our patient populations, we also need to stabilize the markets as they currently are," Mr. Melmeyer said. On this front, NORD has encouraged Congress to take a bipartisan approach to try to stabilize the marketplaces. "NORD is encouraged that talks continue within the Senate Health Education and Labor and Pensions Committee," Mr. Melmeyer said. "These are discussions around how we can make sure our current health insurance marketplace is stable." And while Congress has yet to act on any of these stabilization efforts, NORD is still hopeful that legislation can pass, possibly when Congress passes the next omnibus package.

There are several different policy options being considered, including appropriating the cost-sharing reductions. In addition, re-insurance programs are being investigated as an aid to insurers who are incurring higher than expected costs within their specific risk pools, thus driving up premiums since they have to cover that cost. Other mechanisms to stabilize the current insurance market are also being explored. "NORD believes these reforms can be very impactful for those with rare diseases who are currently purchasing insurance," Mr. Melmeyer said. "Right now we are going in the wrong direction, but we hope to go back in the right direction with these stabilization proposals."

Tax Reform

In October, the big initiative ongoing within Congress was tax reform. Why would NORD be involved in tax reform? "It could be very impactful to us because of the Orphan Tax Credit," Mr. Melmeyer said. The Orphan Drug Tax Credit is one of the incentives that was passed as part of the Orphan Drug Act back in 1983. According to Mr. Melmeyer, It can be credited for about 33% of the orphan drugs that have been developed in the past 35 years and about one third of the orphan drugs going forward. "It is that strong of an incentive for companies to enter into the orphan drug market." The methods that the government proposed in its preliminary tax reform legislation is called zero-base tax reform, which means that they wipe out all business credits and then build up from there. "The original tax reform proposal eliminated all tax credits except two—the low-income tax credit and the research and development tax credit. This would mean that the Orphan Drug Tax Credit would be repealed. It would no longer be in existence and we would see one-third fewer orphan drugs going forward if that proposal was enacted," Mr. Melmeyer said. This is obviously concerning to NORD. "We do not want to see one third of future orphan drugs disappear overnight. We are trying our best to emphasize to Congress just how important this tax credit is to our community. Credit is due to the 140 patient organizations who joined us in a letter to Congress emphasizing the importance of the tax credit."

In the ensuing two months, the House of Representatives proposed a complete repeal of the Orphan Drug Tax Credit as part of their Tax Cuts and Jobs Act, and the Senate proposed to cut the credit nearly in half. NORD led the charge against these proposals by coalescing the rare disease patient community in opposition. Thousands of letters were sent from the community to Congress, hundreds of phone calls were placed, the #SaveOrphanDrugs campaign launched, and patients and patient representatives visited their Senators to urge them to maintain the credit. When the tax reform legislation was enacted into law in mid-December, the credit had been cut in half. While this was not the optimal result, the community was able to successfully avoid a full repeal of the credit, and the credit will remain an important incentive for orphan development.

21st Century Cures Act and FDARA

The 21st Century Cures Act and the Food and Drug Administration Reauthorization Act (FDARA) are two landmark pieces of legislation that passed in the last year or so. "It was fantastic that they were passed. Now we have to implement them," Mr. Melmeyer said. "There are going to be a lot of decisions that are going to be made at the FDA over the course of the next several years on how best to implement the provisions within these laws. There are several that come to mind as being important for NORD and for our patient communities to be engaged in. For example, FDA decisions on how best to involve patients in clinical trials, how to collect patient experience data, how to collect patient preference data, how to collect real world evidence and patient reported outcomes—all sorts of initiatives that the FDA has already launched or will soon be launching around these 21st Century Cures Act and FDRA provisions." Over the next several years, the FDA will likely hold public meetings on their initiative proposals. Mr. Melmeyer encouraged patients and patient organizations to attend these meetings and voice their opinions on open questions, such as what do you want the FDA to do? How do you want to be involved? What questions should the FDA be asking as we try to collect data on what it is like to be a patient with a specific disease?

Orphan Drug Modernization Plan

Other federal initiatives that NORD is focused on are the Orphan Drug Modernization plan and the creation of an FDA Office of Patient Affairs. "For those who may want to get involved with the FDA initiatives but do not know where to start or who to call first, this office is meant to be a liaison, to act as a navigator, to help patients and patient organizations navigate all the different FDA offices and initiatives," Mr. Melmeyer explained. "NORD is excited about that possibility. We want to be sure that it is implemented appropriately, it has the correct staffing, and that all the other patient offices are still maintained and still doing good work."

Much of these hopes have come to fruition. The new Patient Affairs Staff within the Office of Medical Products and Tobacco are serving this exact purpose. They are already putting forward opportunities for patient involvement, such as the Patient Engagement Collaborative, and are working to coordinate patient involvement across the three medical centers. NORD is excited to partner with the new team, and is looking forward to what it will accomplish in the months and years ahead.

Medical Nutrition Equity Act

NORD also will be supporting the enactment of the Medical Nutrition Equity Act. This bill levels the playing field for access to medical nutrition and improves insurance coverage for medical nutrition. NORD was successful in late 2016 in expanding medical nutrition coverage within the TRICARE Program "But now we have to think about Medicare, Medicaid, and private insurance, the VA System, and the federal employee benefits program," Mr. Melmeyer said. "All insurers who are not currently covering medical nutrition right now really need to be covering it. It is medically necessary, just as many prescription therapies are."

Expanded Access to Pre-Approval Therapies and Right to Try

NORD will be working to improve access to pre-approval therapies. "These are therapies that are currently within the clinical trials process," Mr. Melmeyer said. Right now the Expanded Access Program is available to individuals who do not qualify for inclusion in a clinical trial but are seeking access to an investigation therapy. That program works for a lot of people, but it could probably work for more people," Mr. Melmeyer said. "NORD wants to see how we can encourage companies to offer more therapies through Expanded Access, perhaps by lowering the financial disincentives that they currently have. The goal of the Right to Try Act, a related piece of legislation, is exactly this—to expand access to investigational therapies in clinical trials for those who do not qualify for the trial. "What we see in the Right to Try bill is a policy that does not really get at the problem," Mr. Melmeyer said. "It is not the FDA that is holding up access to investigational therapies, it is mostly companies who, for any number of reasons, may not want to provide their product outside of a clinical trial."

That's where NORD sees the most opportunity to develop policy is in—around ways to encourage companies to offer therapy outside of clinical trials for those who would qualify and then also to look at some of the other pieces, such as IRBs and lack of education around access to investigational therapies to see what we can do to try to further that access for individuals seeking investigational therapies.

Value Assessment Frameworks

Finally, there has been plenty of discussion around value assessments and value assessment frameworks and how to value a therapy. Of course most of us are familiar with

the Institute for Clinical and Economic Review and many other value assessment framework developers who are trying to quantify the value of a therapy and compare it to its price. The problem is that oftentimes they are not really taking into account patient viewpoints, they are not including many important quality of life improvements, and they are not really considering the improvements these therapies can have on people outside the people who are taking them, like a parent or a sibling or a caretaker. These are things that we need to emphasize to those who are making value assessment frameworks. This needs to be done responsibly. We need to be careful to not limit access to truly innovative therapies through irresponsible evaluations.

CADASIL: The Migraine–Stroke–Dementia Connection

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Preventive Measures for Sequelae of CADASIL

Stroke. Primary prevention includes careful monitoring and management of cardiovascular risk factors and secondary stroke prevention, including single antiplatelet therapy with aspirin or clopidogrel; dual-antiplatelet therapy has been reported anecdotally. Cerebral microbleeds may or may not occur in CADASIL patients, although the risk of hemorrhage is increased with the use of oral anticoagulation.[13]

Migraine. For prophylaxis of migraine, lifestyle modifications, acetazolamide, vitamin B supplementation, or a selective serotonin reuptake inhibitor are potentially of help.[12]

Cognitive decline. No direct recommendation has been elucidated from clinical trials of treatments for cognitive decline in CADASIL. Donepezil (an acetylcholinesterase inhibitor) was used for 18 weeks in 168 CADASIL patients without effect on the primary endpoint, assessed by cognitive evaluation (using the cognitive subscale of the Vascular Dementia Assessment Scale); some improvement in executive function was noted, however (secondary endpoint).[14]

Summary

Although CADASIL is a rare condition, it is the most common monogenic cerebral small-vessel disease, in which three of the most disabling neurological conditions converge: migraine, stroke, and dementia. *Notch3* gene mutations continue to be identified in multiple populations of different geographic origin and race. Continued study of this condition could bring hope for better understanding and development of effective therapeutic options.

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Deliver Enzyme Replacement Therapy in a 'Trojan Horse' for Hurler Syndrome

Engineering a biologic drug to cross the blood–brain barrier has stymied researchers and drug developers. Will efforts to refine "Trojan horse" technology—using a monoclonal antibody against an endogenous receptor transporter at the blood–brain barrier—overcome this obstacle?

William M. Pardridge, MD

Hurler syndrome, or mucopolysaccharidosis Type I (MPSI), is an inherited autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding the lysosomal enzyme α-L-iduronidase (IDUA).[1] Loss of IDUA function leads to the progressive accumulation of lysosomal storage deposits comprising heparan sulfate and dermatan sulfate glycosaminoglycans.

Most patients with MPSI have severe disease of the central nervous system (CNS); this is the group is designated as Hurler syndrome or MPSIH.[2] A minority of MPSI patients have attenuated CNS disease, designated Hurler-Scheie or Scheie or MPSIatt. The severity of MPSI depends on the type of mutation of the *IDUA* gene on both alleles.

Disease Distinctions and Treatment Limitations

The distinction between MPSIH and MPSIatt is important because treatment differ for the two forms of MPSI.[3] Standard therapy for MPSIatt is weekly intravenous (IV) enzyme replacement therapy with recombinant IDUA (laronidase; Aldurazyme). However, the problem with conventional enzyme replacement therapy is that the enzyme, a large molecule, does not cross the blood–brain barrier or penetrate the brain from blood.[4] Therefore, IV enzyme replacement therapy for MPSI, or for any other lysosomal storage disorder that affects the CNS, does not treat the brain or spinal cord.

Standard therapy for MPSIH is hematopoietic stem cell transplantation, providing the patient has a clinical diagnosis of MPSIH, is younger than 2 years, and has a developmental quotient (DQ), which is an age-adjusted IQ, that is greater than 70.[3] Stem cell transplantation is said to stabilize the decline in DQ in MPSIH, provided stem cell transplantation is performed before 2 years of age. However, an analysis of the effect of stem cell transplantation on CNS function in MPSIH shows that stabilized cognitive function was observed under the conditions that 1) the patient had an initial high DQ of greater than 85 and 2) stem cell transplantation was performed before 16 months of age.[5]

The rationale for treating the CNS in MPSIH with stem cell transplantation is based on the assumption that hematopoietic stem cells cross the blood–brain barrier and populate the brain following IV infusion of the cells. Stem-cell transport across the blood–brain barrier has not been demonstrated experimentally, and animal studies show that stem cells do not cross the blood–brain barrier. In the mouse, stem-cell penetration of the brain is confined to the perivascular spaces of the meninges, which has no blood–brain barrier, without penetration of the parenchyma behind the blood–brain barrier.[6]

In a mouse model of MPSIH, stem cells permanently transfected with a lentivirus encoding IDUA were administered IV, and stem cell penetration of the brain was measured by polymerase chain reaction detection of the viral

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genome in the brain.[7] By this measure, stem-cell penetration of the brain was a background level, and as much as three orders of magnitude lower than stem-cell penetration into peripheral tissues.

These considerations show that the blood–brain barrier is the limiting factor in the treatment of MPSI with stem cell transplantation and with conventional enzyme replacement therapy. What is needed is a new therapeutic approach that deals directly with the blood–brain barrier, so that the IDUA enzyme can be delivered to the parenchyma of brain in patients with MPSI.

New Delivery Option: Trojan Horse Technology

Recombinant protein therapeutics, such as IDUA, can be re-engineered to penetrate the brain via receptor-mediated delivery across the human blood–brain barrier. This is possible with *molecular Trojan horse technology*.[8] A molecular Trojan horse is a monoclonal antibody (MAb) against an endogenous receptor transporter at the blood–brain barrier, such as the human insulin receptor (HIR) or transferrin receptor (TfR). The blood–brain barrier HIR or TfR normally delivers circulating insulin or transferrin across the blood–brain barrier, for brain penetration. Similarly, the blood–brain barrier HIR may also transport a receptor-specific MAb, designated HIRMAb, providing the antibody 1) binds an exofacial epitope on the blood–brain barrier receptor, and 2) is an endocytosing antibody. Once the biologic drug developer is in possession of genes encoding the heavy chain and light chain of the Trojan horse antibody, it becomes possible to engineer a novel IgG-enzyme fusion protein.

A fusion protein of the genetically engineered HIRMAb and human IDUA has been engineered, and is variably designated the HIRMAb-IDUA fusion protein,[9] AGT-181, or valanafusp alpha. The IDUA enzyme is genetically fused to the carboxyl terminal of each heavy chain of the HIRMAb (see Figure). Valanafusp alpha is a bifunctional IgG-IDUA fusion protein, in which the enzyme domain expresses a level of IDUA enzyme activity comparable to laronidase, and the HIRMAb domain binds the HIR with the same high affinity as the original HIRMAb.[9]

The IDUA domain of the fusion protein incorporates mannose 6-phosphate (M6P), which makes the fusion

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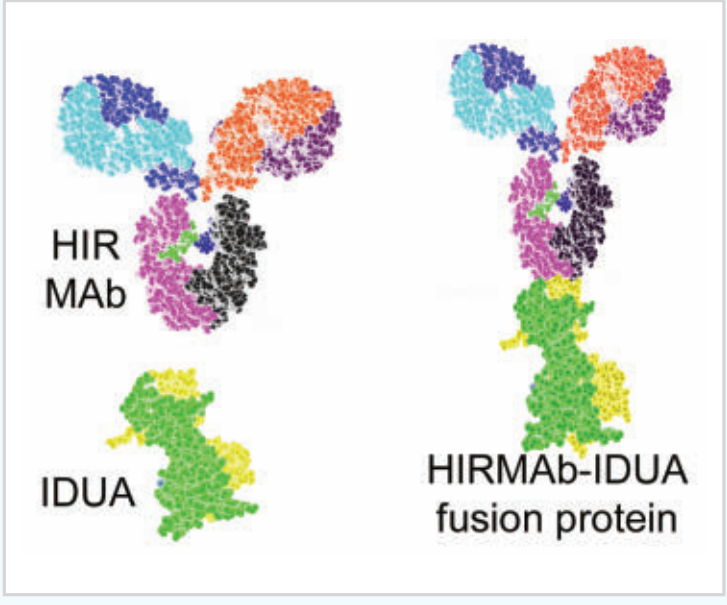
FIGURE: Fusion of iduronidase to each heavy chain of the human insulin receptor monoclonal antibody Trojan horse[8]



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Deliver Enzyme Replacement Therapy in a 'Trojan Horse' for Hurler Syndrome

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protein a ligand for the M6P receptor (M6PR).[4] Valanafusp alpha therefore targets dual receptors: the HIR via the HIRMAb domain of the fusion protein, and the human M6PR via the IDUA domain of the fusion protein. Targeting of the HIR is important for treatment of the brain because, although the blood–brain barrier expresses an insulin receptor, the human blood–brain barrier does not express the M6PR.[4] Lack of M6PR expression on the human blood–brain barrier is the singular reason that conventional enzyme replacement therapy does not treat the brain.

The dual receptor targeting properties of valanafusp alpha is shown in whole-body autoradiography in the adult rhesus monkey following IV administration of either [I^{125}]-laronidase or [I^{125}]-valanafusp alpha.[4] There is comparable uptake of laronidase and valanafusp alpha by peripheral organs, because both proteins penetrate these organs via uptake mediated by the M6PR, which is a more active peripheral clearance mechanism than the HIR.[10] However, there is no uptake of laronidase by the primate brain, owing to the absence of the M6PR at the blood–brain barrier.[4] Conversely, there is robust uptake of valanafusp alpha by the monkey brain, owing to the expression of the insulin receptor on the blood–brain barrier.[4] Treatment of the 6-month old Hurler mouse for eight weeks with 1 mg/kg IV Trojan horse-IDUA fusion protein produces a greater than70% decline in lysosomal inclusion bodies in the brain.[11]

> Treatment of the CNS in MPSI is a model of what can be done for other lysosomal storage disorders that affect the brain.

Accumulating Experience and Continuing Investigation

Valanafusp alpha has been developed for the treatment of humans with MPSI. Lack of systemic toxicity has been reported for monkeys administered as much as 30 mg/kg valanafusp alpha for six months.[9] Hypoglycemia was observed in monkey administered the 30 mg/kg dosage by rapid IV infusion in saline;[12] however, this dosage is 10-fold greater than the human therapeutic dose, and hypoglycemia in primates was eliminated by fusion-protein infusion in saline with dextrose.[12] At the end of six months of chronic treatment with 3 to 30 mg/kg of valanafusp alpha, an end-of-study IV glucose tolerance test showed no impairment of glycemic control in primates.[12]

An investigational new drug application for treatment of MPSI with valanafusp alpha (AGT-181) was approved by the FDA in 2015; a phase I-II clinical trial of this new treatment for the brain and peripheral organs of MPSI pediatric patients was initiated in Brazil.[13] The patients in this trial have been treated for longer than one year with weekly IV infusion of valanafusp alpha; the combined incidence of hypoglycemia and allergic infusion reaction is less than 5%. All patients treated with valanafusp alpha had severe CNS impairment at enrollment (average DQ, <40).

The next step in the development of valanafusp alpha as a new treatment for the brain in MPSI is a phase III clinical trial.

Applying What Has Been Learned to New Challenges

Treatment of the CNS in MPSI is a model of what can be done for other lysosomal storage disorders that affect the brain (there are more than 50 lysosomal storage disorders; approximately 75% affect the CNS). None of the recombinant lysosomal enzymes cross the blood–brain barrier, and, as noted, it is impossible to treat the CNS with conventional IV enzyme replacement therapy.

Attempts have been made to deliver the recombinant enzyme to the brain via intrathecal injection into the cerebrospinal fluid, but this approach for drug delivery to brain parenchyma is limited. Drug injection into the cerebrospinal fluid is equivalent to slow IV infusion, as the drug moves rapidly from the cerebrospinal fluid to the blood via the natural bulk flow of cerebrospinal fluid.[14] This rate of bulk flow of cerebrospinal fluid is rapid compared to the slow rate of enzyme diffusion into the brain parenchyma from the cerebrospinal fluid compartment.[14] Consequently, intrathecal drug delivery to the brain allows for drug distribution only to surface of the brain at the brain–cerebrospinal fluid interface—particularly in humans, in whom the diffusion distance is logarithmic orders of magnitude greater than diffusion distances in the brain of smaller animals.[14]

The lysosomal enzyme drug developer can re-engineer the lysosomal enzyme for blood–brain barrier drug delivery using molecular Trojan horse technol-

ogy. Lysosomal enzymes other than IDUA have been re-engineered as IgG-enzyme fusion proteins, including iduronate 2-sulfatase for MPS type II; N-sulfoglucosamine sulfohydrolase for MPS type IIIA; alpha-N-acetylglucosaminidase for MPS type IIIBl; and arylsulfatase A for metachromatic leukodystrophy.[8]

The difficulty experienced by lysosomal enzyme drug developers in treating the brain goes beyond orphan drug development, and extends to all diseases of the CNS. Today, there is not a single biologic that is FDA-approved for treatment of a brain disorder, wherein the biologic must cross the blood–brain barrier.

The delay in biologic drug development for CNS disease is a natural result of 1) the lack of blood–brain barrier transport of biologics and 2) the nascent effort by the pharmaceutical industry to develop blood–brain barrier drug delivery technology that can be translated to the clinic. Development of valanafusp alpha for treatment of the brain in MPSI is a model of what can be done in the future—not only for orphan diseases that affect the brain but, potentially, for any CNS disease that is treatable with a recombinant therapeutic protein.

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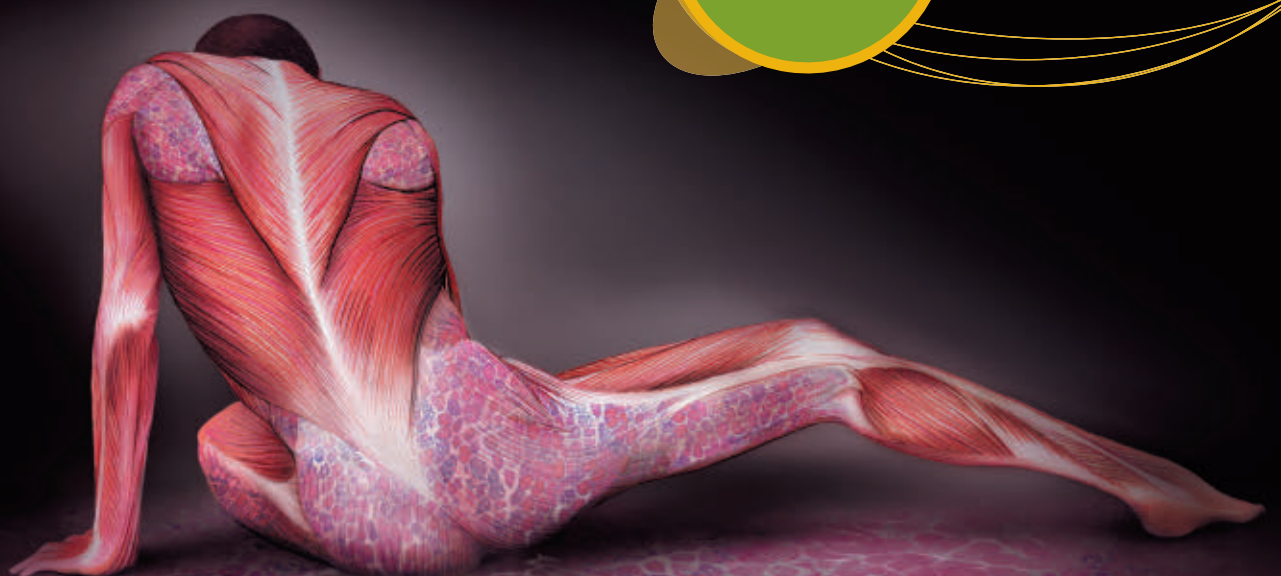

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