

NEUROLOGICAL RARE DISEASE SPECIAL REPORT

FEBRUARY 2015



NORD
National Organization for Rare Disorders

NEUROLOGY
REVIEWS®

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Ready to Fight

ONFI® (clobazam)™ is FIERCELY DEDICATED to helping Bobby & Julian fight their seizures.

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



Learn more about how ONFI can be an effective part of your LGS treatment regimen at ONFIhcp.com.

Julian, age 6,
diagnosed with LGS.



Important Safety Information

- 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 (CNS) depressants. Prescribers should 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.
- ONFI has a CNS depressant effect. Patients should be cautioned against the simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated.
- As with all antiepileptic drugs (AEDs), ONFI should be gradually withdrawn to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. Withdrawal symptoms have been reported following abrupt discontinuation of ONFI; the risk of withdrawal symptoms is greater with higher doses.
- Serious dermatological 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. ONFI should be discontinued at the first sign of rash, unless the rash is clearly not drug-related.
- 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. 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.
- AEDs, including ONFI, increase the risk of suicidal thoughts or behavior in patients. Patients, their caregivers, and families should be informed of the risk and advised to monitor and report any emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or 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.
- The most commonly observed adverse reactions reported in an LGS randomized, double-blind, placebo-controlled, parallel group clinical trial who received clobazam as adjunctive therapy ($\geq 10\%$ 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%), drooling (14% vs. 3%), aggression (14% vs. 5%), irritability (11% vs. 5%), ataxia (10% vs. 3%), and constipation (10% vs. 0%).

Please see Brief Summary of Prescribing Information on the following pages. For full Prescribing Information, Medication Guide, and Instructions for Use go to www.ONFI.com.

ONFI® (clobazam) tablets, for oral use, ©
ONFI® (clobazam) oral suspension, ©

Brief Summary of Prescribing Information

(See package insert for full Prescribing Information or visit www.ONFI.com)

Rx Only

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.

CONTRAINDICATIONS – None [see *Contraindications*].

WARNINGS AND PRECAUTIONS – 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 [see *Warnings and Precautions*]. **Potential 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 *Warnings and Precautions*].

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 [see *Dosage and Administration*]. 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 *Warnings and Precautions*].

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 *Warnings and Precautions*].

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*].

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*].

ADVERSE REACTIONS – 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*]. 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 in the full Prescribing Information 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

	Placebo N=59 %	ONFI Dose Level			All ONFI N=179 %
		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; **Investigations:** Hepatic enzyme increased; **Musculoskeletal:** Muscle spasms; **Psychiatric Disorders:** Agitation, anxiety, apathy, confusional state, depression, delirium, delusion, hallucination; **Respiratory Disorders:** Aspiration, respiratory depression; **Skin and Subcutaneous Tissue Disorders:** Rash, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), urticaria.

DRUG INTERACTIONS – Effect of ONFI on Other Drugs: 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, Patient Counseling Information*]. ONFI inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary [see *Clinical Pharmacology*]. **Effect of Other Drugs on ONFI:** 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 coadministered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) [see *Clinical Pharmacology*]. **CNS Depressants and Alcohol:** Concomitant use of ONFI with other CNS depressants may increase the risk of sedation and somnolence [see *Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS – Pregnancy - 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/>. **Pregnancy Category C:** There are no adequate and well-controlled studies of ONFI in pregnant women and no adequate developmental toxicity studies of clobazam in animals. Although limited, the available animal data suggest developmental toxicity, including an increased incidence of fetal abnormalities following oral administration of clobazam to pregnant animals at doses similar to those used clinically. Data for other benzodiazepines suggest the possibility of adverse effects in animals and humans. Long-term effects on neurobehavioral and immunological function have been reported in rodents following prenatal exposure to benzodiazepines. Neonatal flaccidity, respiratory and feeding difficulties, hypothermia, and withdrawal symptoms have been reported in infants born to mothers who received benzodiazepines, including clobazam, late in pregnancy. Therefore, ONFI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations*]. **Nursing Mothers:** ONFI is excreted in human milk. The effects of this exposure on infants are unknown [see *Use in Specific Populations*]. **Pediatric Use:** The 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, Clinical Pharmacology*]. **CYP2C19 Poor Metabolizers:** Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, the initial dose in patients known to be CYP2C19 poor metabolizers should be 5 mg/day. Dose titration should proceed slowly according to weight to 10-20 mg/day, and may be titrated further to a maximum daily dose of 40 mg on day 21 based upon clinical response [see *Dosage and Administration, Clinical Pharmacology*]. **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, Clinical Pharmacology*]. **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, the initial dose in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9) should be 5 mg/day. These patients should be titrated according to weight to 10 to 20 mg/day, and may be titrated further to a maximum daily dose of 40 mg on day 21 based upon clinical response. There is inadequate information about metabolism of ONFI in patients with severe hepatic impairment. Therefore no dosing recommendation in those patients can be given [see *Dosage and Administration, Clinical Pharmacology*].

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*]. **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. **Withdrawal:** Abrupt discontinuation of ONFI causes withdrawal symptoms. As with other benzodiazepines, ONFI should be withdrawn gradually [see *Dosage and Administration, Warnings and Precautions*]. 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 [see *Warnings and Precautions*]. 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 *Warnings and Precautions*].

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 [see *Overdosage*]. **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 [see *Management of Overdosage*].

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Deerfield, IL 60015, U.S.A.

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Glenn S. Williams

EDITOR'S NOTE

Frontline Medical Communications, the parent company of *Neurology Reviews*, and the National Organization for Rare Disorders (NORD) have joined together in a strategic partnership to develop innovative educational programs for health care providers. The goal is to increase awareness of rare diseases among

health care professionals and ultimately reduce the time to diagnosis and treatment of rare diseases. Individually, these diseases are rare; collectively rare diseases affect nearly 30 million Americans. The average time to diagnosis of a rare disease is about seven years. Through a targeted outreach to health care professionals, we hope to better serve the rare disease community.

This Special Report, published in February to coincide with Rare Disease Day (February 28), collects and highlights *Neurology Reviews'* recent coverage of rare neurologic diseases. This is an ongoing effort. *Neurology Reviews* and other Frontline publications will provide continuing coverage of rare diseases.

—Glenn S. Williams

Vice President, Group Editor
Neurology Reviews



Peter L. Saltonstall

A NOTE FROM NORD

For more than 30 years, the **National Organization for Rare Disorders (NORD)** has served as the hub for the rare disease community, providing advocacy, education, patient assistance programs, and other services on behalf of all patients and families affected by rare diseases.

While great progress has been made, it has become increasingly apparent in recent years that people with rare diseases often wait far too long for a diagnosis and treatment. With 7,000 diseases considered rare in the US, many of which are multisystem and/or complex, the diagnostic challenge is daunting. However, we have been greatly encouraged by growing interest in rare diseases, and we look forward to working with Frontline to serve the medical community—and, therefore, our patients and families—with up-to-the-minute information about rare diseases and helpful resources.

—Peter L. Saltonstall

President and CEO
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Why Should We Care About Rare Disease Day?

By Jess Thoene, MD

Emeritus Professor of Pediatrics at the University of Michigan



Rare Disease Day (Feb. 28) is upon us. Why should we, as physicians, care? There are a large number of well-established reasons why any practitioner should be aware of the unusual (rare) conditions that may occur in her or his practice. The most compelling is that although rare diseases are, by definition, rare, collectively, they affect almost 30 million Americans. And in some cases, they are treatable. Thus, to miss the correct diagnosis and, therefore, deny needed life-saving or quality of life-improving treatment is a grave concern. How best to avoid this professional scotoma?

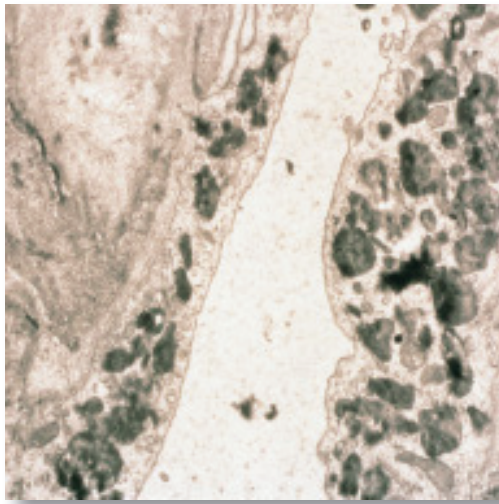
Resources exist to assist in identifying an appropriate differential, including rare diseases, and any available treatment for a given rare condition. Websites, including those of the National Organization for Rare Disorders (NORD) (www.rarediseases.org), the NIH Office of Rare Disease Research (www.rarediseases.info.nih.gov), and the FDA Office of Orphan Products Development (www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm) can assist the clinician in assessing possible diagnoses and appropriate therapy. If that fails, the NIH Undiagnosed Diseases Program (www.rarediseases.info.nih.gov/research/pages/27/undiagnosed-diseases-program), recently expanded to a network of seven satellite centers around the US (see page S15), provides robust chart review and diagnosis, up to and including new disease discovery. NORD has a program to pay for baseline medical testing for applicants to this NIH program whose insurance will not cover this testing. Beyond that, the NIH Rare Diseases

Clinical Research Network (www.rarediseases.info.nih.gov/research/pages/41/rare-diseases-clinical-research-network) offers specialized rare disease centers across the nation to support diagnosis and treatment of a wide variety of rare conditions.

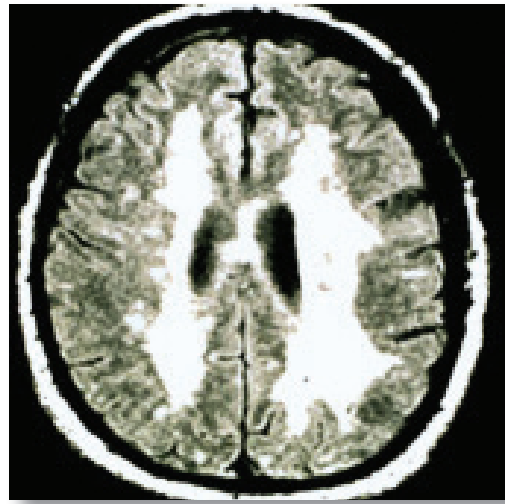
Much progress has been made since the passage of the Orphan Drug Act (PL 97-414) of 1983 (see page S6). At that time, there were only 10 products brought to market by industry that today would be recognized as treatments for rare diseases. Currently, the FDA has approved more than 450 orphan products, and many more have received orphan designation and are pending New Drug Approval (see page S44).

Regrettably, much remains to be done. With 7,000 identified rare diseases, but only a few hundred approved therapies, the situation remains bleak for most patients with rare diseases. Worse, a subtle prejudice against rare conditions in favor of common ones remains evident. An Op-Ed in the *New York Times* of Jan. 5, 2015 (“Stop Subsidizing Big Pharma,” by Llewellyn Hinkes-Jones) on the high cost of drugs included this statement: “Efforts to cure, rather than treat or prevent, obscure diseases can be expensive, diverting investment from more common afflictions.” This represents the essence of the rare disease dilemma: in a world of limited resources, is it better to ignore the few in order to better to serve the many? The National Organization for Rare Disorders says, “No, we must strive to do both.” A good way to proceed to accomplish this end is through better physician awareness of rare disorders.

If you see premature stroke in a patient It could be **FABRY DISEASE**



Progressive accumulation of substrate in the vascular endothelium leads to ischemia and infarction of these vessels.



White matter lesions on MRI, demonstrating evidence of cerebrovascular infarct.
Image courtesy of Edward M. Kaye, MD.

In addition to premature stroke, patients with Fabry disease may present with:

- Transient ischemic attacks
- Neuropathic pain (“burning” pain in the hands and feet)
- Hypohidrosis
- Heat/cold and exercise intolerance
- Hearing loss, tinnitus
- Vertigo/dizziness
- Nystagmus

Other manifestations include:

- Progressive and/or unexplained chronic kidney disease
- Premature cardiac disease
- Corneal and lenticular abnormalities (seen through slit lamp—generally does not affect vision)
- Angiokeratomas (reddish-purple skin lesions that do not blanch with pressure)
- Gastrointestinal problems

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Rare Diseases Are Not So Rare in Neurology

Tackling rare neurologic diseases is a formable task, but new tools are available to aid in the fight to prevent and treat these devastating disorders.



Darryl C. De Vivo, MD

PHILADELPHIA—In neurology, rare diseases are not so rare. In fact, they are pretty common. “Essentially every patient who comes to see me in my office has a rare disease,” said Darryl C. De Vivo, MD, in his presidential plenary lecture on rare diseases and neurologic phenotypes at the 66th Annual Meeting of the American Academy of Neurology.

Dr. De Vivo is the Sidney Carter Professor of Neurology, Professor of Pediatrics, and Director Emeritus of the Pediatric Neurology Service at the Columbia University Medical Center in New York City. He is also the Associate Chairman for Pediatric Neurosciences and Developmental Neurobiology, the Founding Director of the Colleen Gibling Research Laboratories for Pediatric Neurology at the Columbia University Medical Center, and the Codirector of the Center for Motor Neuron Biology and Disease.

Rare Diseases—The Basics

Dr. De Vivo outlined some basic facts and statistics regarding rare diseases. “Obviously, each rare disease is rare by definition, but collectively, they are common.” Rare diseases are generally inherited as recessive traits, and most have a neurologic phenotype. A rare disease, as defined by the Orphan Drug Act of 1983, is a condition that affects fewer than 200,000 Americans. “That’s a considerable number,” Dr. De Vivo said, “when you consider that rare diseases range from affecting just one person to several thousand, but on average a rare disease affects about 4,000 people.” About 7,000 rare diseases are known and are listed on the NIH Office of Rare Diseases’ website (<http://rarediseases.info.nih.gov>).

Approximately two-thirds of rare diseases affect children but are “not limited to child neurology because these children often grow to adulthood, and some rare diseases do not become symptomatic until the adult period,” Dr. De Vivo said. About 80% of rare diseases are caused by genetic mutations. Approximately 25 to 30 million Americans have a rare disease, according to Dr. De Vivo, which equates

to about 8% to 10% of the American population. He also noted that only 5% of the 7,000 known rare diseases have FDA-approved treatments.

A Brief History of a Rare Disease—Glut1 Deficiency

Dr. De Vivo chose Glut1 deficiency as the quintessential example of a rare disease. Glut1 deficiency was described 23 years ago in two infants who had a neurologic phenotype. Investigators assumed then that a fundamental defect existed in the transport of glucose from the blood into the brain. Knowing that ketones are the only alternative source of oxidizable fuel for brain metabolism, researchers recommended the ketogenic diet as the symptomatic treatment, and it remains the standard of care today.

Seven years after its first description, pathogenic mutations were identified in the Glut1 gene, or more specifically, the *SLC2A1* gene. During the ensuing years the phenotypic variability of Glut1 deficiency has continued to expand and now includes various epileptic conditions, movement disorders, degrees of intellectual disability, and milder persistent paroxysmal variants. It is now estimated that in the United States, the prevalence of Glut1 deficiency is at least 3,150 cases, which is close to the average prevalence of 4,000 cases for the 7,000 known rare diseases.

In 2006, a mouse model was developed to further explore Glut1 deficiency and to investigate possible therapeutic interventions. It became clear that dystonia 18 was an allelic variant of Glut1 deficiency. In 2011, researchers noted that dystonia 9 was also an allelic variant.

Regarding the first two patients, Dr. De Vivo said “both infants presented with an epileptic phenotype in early infancy that contributed to their developmental delay and led to a disturbance in postnatal brain development, deceleration of head growth, and acquired microcephaly.” Both patients had evidence of low CSF glucose and low CSF lactate, which “has

Rare Diseases Are Not So Rare in Neurology

continued

turned out to be a critically important diagnostic biomarker to identify this population of patients.” Because the red blood cell membrane is enriched with the Glut1 protein, transport of glucose into the patient’s red blood cells serves as an effective functional assay to identify patients with Glut1 deficiency.

“Since those first two patients, we’ve seen about 150 patients, and others have seen at least that number, if not more,” Dr. De Vivo said. “In every case, we have found that the CSF glucose and the CSF lactate values have been informative. The lumbar puncture is essentially diagnostic.” About two-thirds of patients with low CSF glucose and lactate have a definable disease-causing mutation in the *SLC2A1* gene. “But more importantly, about 90% of the CSF glucose values fall below 40 mg/dL or 2.2 mmol/L. About two-thirds of the CSF lactate values fall below 1 mmol/L.”

“Obviously, each rare disease is rare by definition, but collectively, they are common.”

—Darryl C. De Vivo, MD

Haploinsufficiency determines the pattern of inheritance in patients with Glut1 deficiency. The rate of glucose uptake by the patient’s red blood cell is a surrogate for the degree of haploinsufficiency. “More than 90% of the patients we’ve seen have one normal allele and one null allele, and the red blood cell uptake assay has a value of about 50% compared with controls. In a smaller percentage—well below 10% at this point in time—we have identified some patients who have recessive mutations in the Glut1 gene.”

An Evolving Phenotype

Glut1 deficiency also is instructive in the context of rare diseases because its clinical phenotype changes during development. “Developmental delay, to a greater or lesser degree, affects 100% of these patients, as does developmental clumsiness and ataxia,” Dr. De Vivo said.

“This is a lifelong disability that these patients have,” he added. “The epileptic phenotype is largely limited to infancy. You see it in about 90% of the patients with Glut1 deficiency, and then it gradually subsides through childhood, adoles-

cence, and into early adulthood. In contrast, the movement disorder, dominated principally by dystonia, emerges from late infancy and early childhood, up through adolescence, so that about 100% of patients with Glut1 deficiency known to exist demonstrate persistent or paroxysmal dystonia.”

Gene Therapy

“We have now started investigating more effective disease-modifying therapies to treat this condition, starting with experiments involving patients’ cultured human fibroblasts,” Dr. De Vivo said. Using gene therapy strategies in a mouse model, Dr. De Vivo and colleagues have restored Glut1 activity and totally mitigated the motor defect. By restoring Glut1 activity to the mouse model, the researchers were also able to increase the brain expression of Glut1 RNA and Glut1 protein and increase the CSF glucose concentrations from abnormally low values to the normal values of wild-type mice. “We have gotten to the point where we can effectively treat or cure the mouse model of this disease, and now we have to position ourselves to conduct equivalent studies in the human setting,” Dr. De Vivo said.

Take-Home Messages

“It is quite obvious from your own experience and certainly from my experience that rare diseases are common in neurology,” Dr. De Vivo said. “We now have a number of tools with which we can mitigate many of the neurologic phenotypes. Preconception carrier testing is an effective way to prevent untreatable recessive diseases. We can test for more than 100 untreatable recessive diseases, like Tay-Sachs disease, by preconception carrier testing and prevent these diseases from occurring.”

Expanded newborn screening could also make a large impact, “since it would increase the opportunities for proactive treatment of the presymptomatic infant. Early diagnosis and treatment is probably the most important aspect to approaching these patients, as is the case with phenylketonuria, particularly if you can identify the patients from the genotypic point of view before they become phenotypically affected.”

Finally, Dr. De Vivo noted that molecular-based gene therapy is now entering the clinic. “We can now explore the wonderful opportunities that are emerging for gene therapy to rescue the phenotype in our patients who develop neurologic symptoms,” he concluded.

—Glenn S. Williams

CHARCOT-MARIE-TOOTH DISEASE

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Diagnosis and Treatment for Charcot-Marie-Tooth (CMT)

■ **Sean Ekins, PhD, DSc, CSO**
& Allison Moore, CEO
Hereditary Neuropathy Foundation

CMT is a complex disabling inherited rare disease which has multiple genetic causes [1], and affects 1 in 2500 Americans [2], although it may be more prevalent. CMT impairs quality of life and patients suffer from delayed diagnosis and unnecessary treatments. With early and accurate diagnosis, interventions to manage the symptoms can be introduced as well as avoidance of environmental factors and prescribed medications that may exacerbate symptoms.

Relatively simple observations can be useful to lead to a CMT diagnosis. A 2006 study showed that the probability of a patient who has bilateral cavovarus feet will have CMT is 78 % [3]. When there is a family history of the disease this probability increases to 91% [3]. Early signs of the disease present pes cavus and poor reflexes which may pose an obvious diagnosis once the physician is aware of the characteristics. CMT causes awkward gait, foot and hand deformities, muscle atrophy and fatigue, of mostly the calves and hands. Additional tests may help to determine differential diagnosis. Genetic tests are available. Several studies have shown that just 4 genes (PMP22, MPZ, GJB1 and MFN2) can identify those with CMT as over 90% have mutations in these genes [1]. Patients that are negative for these genes can be further evaluated

with nerve conduction velocity testing and exome sequencing.

CMT1A (PMP22 over expression) is the most common form of CMT. As for all forms of CMT, no specific curative or symptomatic medication has been approved. Two recent publications described a novel synergistic combination of 3 drugs already approved for unrelated indications: baclofen, naltrexone and sorbitol [4] [5]. These drugs are combined at new optimal lower doses and under a new formulation. This novel potential therapeutic is called PXT-3003. In preclinical studies, PXT-3003 was shown to lower PMP22 over expression responsible for myelination perturbation in two different CMT1A rodent models [4]. In phase 2, PXT-3003 showed, beyond stabilization, a significant improvement in the ONLS (Overall Neuropathy Limitation Scale) composite score versus placebo. ONLS is considered a major scale to evaluate disability of upper and lower limbs in peripheral neuropathies. PXT-3003 was safe and well tolerated [5]. An international Phase 3 trial will enroll later this year. PXT-3003 may represent a promising approach however there are still steps to pass before it is an approved treatment for CMT1A in the US and Europe.

The Hereditary Neuropathy Foundation (HNF) uses the Therapeutic Research In Accelerated Discovery (TRIAD) as a collaborative model with academia, government and industry, enabling funding of key research

priorities for many forms of CMT. HNF developed the Global Registry for Inherited Neuropathies (GRIN) to collect data on patients who have either been clinically diagnosed by a doctor or genetically diagnosed with a form of CMT or related inherited neuropathy. The registry will provide data to enable the pharmaceutical industry to judge the risk - reward of the patient population for pursuing future clinical trials, obtain a better understanding of the natural history of CMT and evaluate the influence of therapy on patients' quality of life. It is therefore important to encourage patients to enroll in GRIN to help support ongoing clinical studies.

In summary, it is imperative that the early signs of CMT are recognized and patients referred for the management of their CMT symptoms. Currently there is no cure for CMT, but quality of life can improve with physical therapy, occupational therapy, corrective feet and hand surgical procedures, orthotic and AFO's to improve irregular gait and drop foot. The best way to obtain a diagnosis is through detailed patient history, careful physical exam and genetic testing. Differential diagnosis and follow up of epidemiology will help to determine families at greater risk who may benefit from future therapies early on that may improve their CMT symptoms.

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Reflections on the Orphan Drug Act and a Roadmap for Future Success

Representative Henry A. Waxman offers his perspective on the key issues regarding the future development of drugs for rare diseases.

ALEXANDRIA, VIRGINIA—When Representative Henry A. Waxman (D-California) held the first hearing in Congress on rare diseases in 1980, 10 drugs developed by US pharmaceutical companies to treat rare diseases were on the market. Today, three decades after the 1983 passage of the Orphan Drug Act, which Rep. Waxman championed, the FDA has approved more than 450 orphan drugs to treat the more than 25 million Americans living with rare diseases.

To ensure that the accelerated growth of such treatments continues, Congress must increase funding for the NIH, retool current legislation designed to encourage the pharmaceutical industry to undertake more rare disease research of its own, and—above all, in Rep. Waxman’s estimation—come to terms with the high cost of orphan drugs.

“We can celebrate that we’ve accomplished a lot, but there are thousands of rare diseases without treatments,” he said in a keynote address at the National Organization for Rare Disorders (NORD) Rare Diseases and Orphan Products Breakthrough Summit. “The cost of many orphan drugs is still far too high. We need to continue our quest to ensure that the rapid pace of development of orphan drugs continues while preserving patients’ access to these drugs by keeping the price tag at a reasonable level.”

The Hard-Knock Realities of Orphan Disease Drug Development

Excessively high drug prices, including those for orphan drugs, are unsustainable for the US healthcare system, according to Rep. Waxman. Among the examples he cited was Kalydeco (ivacaftor), which the FDA approved in 2012 for the treatment of a rare form of cystic fibrosis and which the Congressman reported costs more than \$300,000 per year. Nearly one-third of orphan drugs net more than \$1 billion in annual sales, he noted.

“In 2012, the leukemia drug Rituxan [rituximab] had sales of over \$7 billion,” Rep. Waxman said. “Another blood cancer drug, Revlimid [lenalidomide], had sales of over \$3.7 billion. And the multiple sclerosis drug Copaxone [glatiramer acetate injection] had sales of over \$4 billion. Perhaps these [prices] would be justified if we looked at the cost of the development of the drugs, but they don’t really compare.... We’re seeing extraordinarily priced drugs bearing no relationship to the cost of their development.”

Driving up the cost of any new drug is the development cost to the manufacturer of previous drugs that did not succeed, which Rep. Waxman believes should be weighed against the savings gained when new drugs are effective. Without these savings, the costs of medical care for patients with orphan diseases would skyrocket.

“I don’t know what the answer is to this problem, but there should be a more rational relationship between the cost of the drug’s development and its price, and this is, of course, not a problem specific to orphan drugs,” he said. “From the perspective of the sustainability of our healthcare system, it’s becoming an even bigger problem with new specialty drugs intended to treat millions of patients.... The poster child of such drugs is Sovaldi [sofosbuvir], which, at \$1,000 a pill costs \$84,000 for a course of treatment for hepatitis C.”

Although Sovaldi’s sales for the first half of this year reached \$6 billion, Rep. Waxman pointed out that it is likely to be superseded by a new combination drug recently approved by the FDA. Harvoni (ledipasvir and sofosbuvir), made by the manufacturer of Sovaldi—Gilead Sciences—will cost around \$94,000 for a full course of treatment.

“These are great drugs, offering a complete cure for people with the most common form of hepatitis C,” he said. “However, when you look at two to three million Americans with this form of hepatitis C, insurers, patients, and Medicaid programs are wondering where they will get the money nec-

Reflections on the Orphan Drug Act and a Roadmap for Future Success

continued

essary to pay for the drugs. If all the people currently eligible for the treatment were to get it, it could cost the US healthcare system well over \$100 billion just for this one disease alone, and clearly this is not sustainable.”

The High Cost of Not Adequately Funding the NIH

Although Rep. Waxman lauds current efforts in Congress to help facilitate the discovery, development, and marketing of new medical therapies as part of the 21st Century Cures Initiative, he emphasized that the most important and consistent recommendation emerging from every one of the hearings related to this issue is that Congress increase its funding of the NIH.

“Everybody agrees with that,” he said, citing NIH Director Francis Collins’s observation that the agency is able to fund one in six research proposals, versus one in three in the past. “We shouldn’t have been proud of one in three. But we should be ashamed that we’re going backward, and it’s now one in six.

“[Dr. Collins] notes that the NIH’s purchasing power has shrunk by 25% over the last decade and he fears that we are in danger of losing a generation of young scientists who no longer see a future in biomedical research,” he continued. “This is something that we’ve got to correct. And rather than talk about all of the new things we can do for the 21st Century Cures Initiative, before we do any of them, we’ve got to fund NIH. It’s critical that we do that and that the resources be there for the NIH to do its job.”

Expressing pessimism about the likelihood that adequate funding will emerge, Rep. Waxman, who is retiring at the end of this term after representing his district in California for 40 years, cited the recent practices of shutting down the federal government and enacting sequestration of funds as principal reasons why the NIH has been left shortchanged when, instead, Congress should have been putting more money into its budget.

“It will be very important to ensure that the legislative proposals in the 21st Century Cures package strike the kind of balance that was so key to the Orphan Drug Act,” he said. “When they look at the legislation and they’re looking at ways to get these cures out faster, we must not compromise the FDA’s standards for approval, and [the legislation] must be carefully tailored to address and clearly identify problems.”

He pointed to a bill under consideration as part of the Cures Initiative that he says falls far short of these goals. Known as the “MODERN Cures Act” (“Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network,” HR 3116),

the bill, its advocates contend, will encourage pharmaceutical companies to develop “dormant” therapies—drugs that show promise as potential treatments for serious illnesses but are not being pursued because of inadequate patent protection. “On its face, this seems a worthwhile goal,” Rep. Waxman said. “However, the way it proposes to accomplish it is by providing 15 years of exclusivity and 15 years of patent protection after approval for any drug that meets certain limited requirements. As one of our witnesses at the hearing on this bill testified, virtually any drug with a novel active ingredient could qualify for this reward.”

In the view of Rep. Waxman, whom the *Nation* labeled “the Democrats’ Eliot Ness” for his tenacious Congressional oversight, the bill gives away too much and will interfere with the goal of making drugs affordable. “[One aim] of this MODERN bill is to have the FDA look at all the different ways that it can permit drugs and devices to go on the market, with different thresholds for them to meet,” he commented. “Congress shouldn’t be in this business of dictating the kind of level of evidence needed to permit drugs and devices to go on the market.

“Congress’s job should be to ensure that the FDA has the regulatory authority needed to make use of the latest scientific advances,” he said. “We should create policies that foster scientific advances, but we should not enact regulatory policies based on how far we wish those advances had progressed.”

—Fred Balzac

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Proposed Diagnostic Criteria Reflect New Understanding of Neuromyelitis Optica

Antibody-negative individuals may meet the criteria for a diagnosis of neuromyelitis optica.

PHILADELPHIA—A proposed revision of the diagnostic criteria for neuromyelitis optica takes into account newly appreciated variations in the disease's clinical presentation. The new criteria, which were presented at the 66th Annual Meeting of the American Academy of Neurology, would offer potential diagnoses for patients who have symptoms but who do not have the serum antibodies usually associated with the disorder.

The document reflects the current understanding of neuromyelitis optica as a spectrum of clinical symptoms, said Dean Wingerchuk, MD, Professor of Neurology at the Mayo Clinic in Scottsdale, Arizona. Neuromyelitis optica spectrum disorder (NMOSD) was identified in 2007, one year after the existing diagnostic criteria were published.

"We wanted to encompass all patients who would have previously been diagnosed as having neuromyelitis optica or NMOSD" in the new guidelines, said Dr. Wingerchuk. A new stratification of patients as antibody-positive or antibody-negative reflects the fact that not all patients are seropositive at presentation, particularly if they present early in the course of the disease; that antibody testing is not available or reliable everywhere; and that as-yet-unidentified antibodies might be implicated in the disorder.

The workgroup that authored the document consisted of 18 members from nine countries. It began its work in 2011. The proposed criteria need to be validated prospectively before they can be adopted widely, noted Dr. Wingerchuk, who was a primary author of the 2006 criteria.

The current criteria require the presence of transverse myelitis, optic neuritis, and at least two of the following:

- Brain MRI findings that are nondiagnostic for multiple sclerosis (MS)

- A spinal cord lesion extending over three or more vertebral segments
- Seropositivity for NMO-IgG.

The newly proposed criteria include six core characteristics: optic neuritis, acute myelitis, area postrema syndrome (ie, nausea, vomiting, and hiccups), other brainstem syndromes, symptomatic narcolepsy or acute diencephalic syndrome with MRI findings, and symptomatic cerebral syndrome with MRI findings. Antibody-positive patients must have at least one core characteristic to be diagnosed with neuromyelitis optica, and no better explanation for their symptoms should be apparent.

Antibody-negative patients must meet stricter criteria to receive a diagnosis. They must have at least two of the core characteristics and meet the following requirements:

- At least one of the core symptoms must be optic neuritis, myelitis, or area postrema syndrome.
- The core characteristics must be disseminated in space.
- MRI findings must distinguish NMOSD from MS or other demyelinating disorders.

Prospective validation will require follow-up of patients who are seropositive at diagnosis but present with less common syndromes. Validation also will require detailed descriptions of seronegative groups to determine whether they eventually convert to a clinical NMOSD, concluded Dr. Wingerchuk.

—Michele G. Sullivan

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Quantifying the Burden of Illness Among Patients With Narcolepsy



Jed Black, MD

Among patients with narcolepsy, the burden of illness is significant across all age groups, with women experiencing a greater burden of illness than men.

MINNEAPOLIS—Narcolepsy entails a significant burden of illness and is associated with a substantial degree of medical comorbidity and health care burden, according to researchers reporting at the 28th Annual Meeting of the Associated Professional Sleep Societies. Drawing information from the Burden of Narcolepsy Disease (BOND) Database, researchers examined patterns of narcolepsy-associated burden of illness in men versus women and, separately, comorbidity and health care utilization across all adult age categories.

Women Experience a Greater Burden Than Men

A comprehensive, nationwide study found a significant burden of illness among men and women with narcolepsy, although a greater comorbidity burden was observed in women, compared with men. In addition, health care utilization and health plan costs were also higher among women.

Jed Black, MD, Consulting Associate Professor at Stanford University in California, and colleagues used five years of medical claims data to assess a population of 9,312 patients with narcolepsy and 46,559 matched controls. Both males and females with narcolepsy had a significantly greater number of comorbid diagnoses, compared with controls. Regardless of narcolepsy status, odds ratios for almost all comorbidity categories were higher in women, compared with men. This finding was even more pronounced within the narcolepsy cohort. Health care service utilization rates and drug costs were significantly higher

among narcolepsy patients versus controls for both men and women, although utilization of services was higher in female versus male patients.

Age-Related Burden of Illness

Using the same medical claims database and the same patient and control cohorts, Dr. Black and colleagues also examined the burden of narcolepsy across age groups. The greatest prevalence of comorbidities was seen among persons between ages 45 and 54, although the youngest cohort (ages 18 to 24) evidenced the greatest prevalence of anxiety and mood disorders. The percentage excess chronic illness burden (narcolepsy versus controls) was greatest in the 18 to 24 age group (111%), followed by the 25 to 34 age group (94%) and the 35 to 44 age group (85%). Among patients with narcolepsy, diagnoses of anxiety and mood disorders declined with increasing age.

For all age groups, mean annual utilization rates for health care services and non-narcolepsy drugs were approximately doubled, compared with controls, with the greatest excess noted among younger patients with narcolepsy versus controls.

—Glenn S. Williams

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NIH Expands Its Undiagnosed Diseases Network

NIH initiative enrolls new partners in its search for diagnostic tools for rare diseases.

Six new sites recently joined the NIH's Clinical Center in the Undiagnosed Diseases Network (UDN). The network expands the NIH focus on "the rarest of disorders," said Eric D. Green, MD, PhD, Director of the National Human Genome Research Institute, during a July 1, 2014, press conference. The UDN addresses the most difficult-to-solve medical cases and strives to develop effective approaches to diagnose them.

In addition to the current site at the NIH Clinical Center in Bethesda, Maryland, and the Coordinating Center at Harvard Medical School in Boston, the following institutions are now involved:

- Baylor College of Medicine, Houston; principal investigator: Brendan H.L. Lee, MD, PhD
- Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital, Boston; principal investigator: Joseph Loscalzo, MD, PhD
- Duke University, Durham, North Carolina; principal investigators: Vandana Sashi, MD, and David B. Goldstein, PhD
- Stanford University, California; principal investigators: Euan A. Ashley, MD, DPhil, Jonathan Bernstein, MD, PhD, and Paul Graham Fisher, MD
- University of California, Los Angeles; principal investigators: Eric J. Vilain, MD, PhD, Katrina M. Dipple, MD, PhD, Stanley Nelson, MD, and Christina Palmer, CGC, PhD
- Vanderbilt University Medical Center, Nashville; principal investigators: John A. Phillips, III, MD, and John H. Newman, MD

The NIH Common Fund awarded four-year grants of approximately \$7.2 million to each of the six centers. The new sites will conduct clinical evaluation and

scientific investigation in cases that involve patients with prolonged undiagnosed conditions. Physicians within the network will collect and share clinical and laboratory data, including genomic information, clinical observations, and documentation of environmental exposures.

"Newly developed methods for genome sequencing now provide us amazingly powerful approaches for deciphering the causes of rare undiagnosed conditions," said Dr. Green. "Along with robust clinical evaluations, genomics will play a central role in the UDN's mission."

The expanded UDN will be "accelerating discovery and innovation in the way we diagnose and treat patients with previously undiagnosed diseases," added James M. Anderson, MD, PhD, Director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives. "We anticipate the UDN will create a new paradigm in medical diagnostics that will improve our understanding of rare disorders and also generate insight into human biochemistry and physiology of common diseases."

Patients who have undiagnosed conditions can apply to the program. If selected, patients will be brought into one of the network centers for week-long testing. About 3,100 patients have applied, and 750 have been accepted; 60% are adults. Once fully operational, the new sites are each expected to see about 50 patients per year. Applications take about eight to 12 weeks to be evaluated, and there is a waiting list of two to six months to be seen by the multidisciplinary diagnostic team.

Data collected from the patients in the program ultimately will be made available to researchers outside the network, though protocols for data sharing are still being developed.

—Gregory Twachtman and
Glenn S. Williams

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 - Unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the SHARE Program, vision should be assessed at baseline (no later than 4 weeks after starting SABRIL), every 3 months during therapy, and at 3 to 6 months after discontinuing therapy. Once detected, vision loss is not reversible. Even with frequent monitoring, some patients will develop severe vision loss. Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.
 - Because of the risk of permanent vision loss, withdraw SABRIL from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation, and from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation, or sooner, if treatment failure becomes obvious. Periodically reassess patient response and continued need for SABRIL.
 - Do not use SABRIL in patients with, or at high risk of, other types of irreversible vision loss, or, with other drugs associated with serious adverse ophthalmic effects, unless the benefits clearly outweigh the risks. The interaction in these situations has not been well characterized, but is likely adverse.
 - Use the lowest dose and shortest exposure to SABRIL that is consistent with clinical objectives. Adjust the dose in patients with renal impairment.
 - Abnormal magnetic resonance imaging (MRI) signal changes have been observed in some infants treated for IS with SABRIL. These changes generally resolved with discontinuation of treatment, and resolved in a few patients despite continued use.
 - Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts and behavior. Monitor appropriate patients for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
 - As with all AEDs, discontinue SABRIL gradually to avoid withdrawal seizures.
 - SABRIL can cause anemia, peripheral neuropathy, weight gain, and edema. SABRIL can cause somnolence and fatigue. Advise patients not to drive or operate machinery until they know how it will affect them.
 - Vigabatrin is excreted in human milk and may cause serious adverse events in nursing infants. Do not use SABRIL during pregnancy unless the potential benefit justifies the potential risk to the fetus. **Pregnancy Registry:** To provide information regarding the effects of *in utero* exposure to SABRIL, physicians should recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Patients must call the toll-free number 1-888-233-2334 to enroll. Registry information can be found at <http://www.aedpregnancyregistry.org/>.
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 - Adults >16 years of age: fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state
 - Pediatrics 10 to 16 years of age: increased weight, upper respiratory tract infection, tremor, fatigue, aggression, and diplopia
 - In infants, the most common adverse reactions in a controlled clinical study (incidence $>5\%$) were somnolence, bronchitis, ear infection, and acute otitis media.

Please see Brief Summary of Prescribing Information on the following pages.

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Your Partner
in Epilepsy™

for infantile spasms,
to change



Sabril® (vigabatrin) is indicated as adjunctive therapy for patients 10 years of age and older with refractory CPS who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. Sabril is not indicated as a first line agent for CPS.

- In 2 clinical studies in adults, Sabril was superior to placebo in reducing median monthly seizure frequency*
- In a pharmacometric bridging analysis of pooled pediatric data and data from 2 adult studies, weight normalized doses were used to establish efficacy and determine appropriate dosing for patients 10 to 16 years of age with refractory CPS

Sabril is indicated as monotherapy for pediatric patients 1 month to 2 years of age with IS for whom the potential benefits outweigh the potential risk of vision loss.

- The effectiveness of Sabril as monotherapy was established for IS in 2 multicenter controlled studies*

Sabril is 1 of 2 FDA-approved medications with an indication to treat appropriate patients with IS.

*See www.Sabril.net for full study details

Because of the risk of permanent vision loss, Sabril is available only through a special restricted distribution program called **SHARE®** (Support, Help And Resources for Epilepsy). To learn more, go to www.sabril.net, or call toll-free 1-888-45-SHARE (1-888-457-4273).

Please see additional Important Safety Information on the adjacent page.

 **Sabril®**
vigabatrin
500 mg tablet
500 mg powder for oral solution

MAKE THE BOLD DECISION

SABRIL® (vigabatrin) tablets, for oral use

SABRIL® (vigabatrin) powder for oral solution

Brief Summary of Prescribing Information

(See package insert for full Prescribing Information or at www.sabril.net)

WARNING: VISION LOSS

- SABRIL causes permanent bilateral concentric visual field constriction. Because assessing vision may be difficult in infants and children, the frequency and extent of vision loss is poorly characterized in these patients. For this reason, the risk described below is primarily based on the adult experience.
- Based upon adult studies, 30 percent or more of patients can be affected, ranging in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.
- Unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the SHARE program, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Vision assessment is also required about 3 to 6 months after the discontinuation of SABRIL therapy.
- Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- Drug discontinuation should be considered, balancing benefit and risk, if visual loss is documented.
- It is possible that vision loss can worsen despite discontinuation of SABRIL.
- Because of the risk of visual loss, SABRIL should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2-4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.
- The possibility that vision loss from SABRIL may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.
- The lowest dose and shortest exposure to SABRIL consistent with clinical objectives should be used.

Because of the risk of permanent vision loss, SABRIL is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SHARE Program [see *Warnings and Precautions in PI*]. Further information is available at www.sabril.net or 1-888-45-SHARE.

INDICATIONS AND USAGE

Refractory Complex Partial Seizures (CPS)

SABRIL is indicated as adjunctive therapy for adults and pediatric patients 10 years of age and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss [see *Warnings and Precautions*]. SABRIL is not indicated as a first line agent for complex partial seizures.

Infantile Spasms (IS)

SABRIL is indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss [see *Warnings and Precautions*].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Vision Loss

Because of the risk of vision loss, and because, when it is effective, SABRIL provides an observable symptomatic benefit, patient response and continued need for treatment should be periodically assessed.

In patients with refractory complex partial seizures, SABRIL should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time.

In patients with infantile spasms, SABRIL should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment should be discontinued at that time [see **BOXED WARNING**].

Monitoring of Vision

Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is required, unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the Support, Help And Resources for Epilepsy (SHARE) program [see *Warnings and Precautions in full PI*]. Because vision testing in infants is difficult, vision loss may not be detected until it is severe. For patients receiving SABRIL who are not exempted, vision assessment is required at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy and about 3-6 months after the discontinuation of therapy.

For all patients, attempts to monitor vision periodically and/or formal exemptions must be documented under the SHARE program.

Magnetic Resonance Imaging (MRI) Abnormalities in Infants

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with vigabatrin for infantile spasms [see *Pediatric Use for more information*]. The specific pattern of signal changes observed in IS patients was not observed in older pediatric and adult patients treated with vigabatrin for refractory CPS. For adults treated with SABRIL, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population. [see *Warnings and Precautions and Use in Specific Populations in full PI*].

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including SABRIL, 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.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

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 risk did not vary substantially by age (5-100 years) in the clinical trials analyzed (see full PI for absolute and relative risk by indication for all evaluated AEDs). 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 SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. 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.

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually. Patients and caregivers should be told not to suddenly discontinue SABRIL therapy.

In controlled clinical studies in adults with complex partial seizures, SABRIL was tapered by decreasing the daily dose 1000 mg/day on a weekly basis until discontinued.

In a controlled study in pediatric patients with complex partial seizures, SABRIL was tapered by decreasing the daily dose by one third every week for three weeks.

In a controlled clinical study in patients with infantile spasms, SABRIL was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days [see *Dosage and Administration in full PI*].

Anemia

In North American controlled trials in adults, 6% of patients (16/280) receiving SABRIL and 2% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo treated patients, respectively, and a mean decrease in hematocrit of about 1% in SABRIL treated patients compared to a mean gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials in adults and pediatric patients, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials in adults demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

Pooled data from three SABRIL controlled trials in pediatric patients demonstrated that 6% (10/165) of SABRIL patients experienced somnolence compared to 5% (5/104) of placebo patients. In those same studies, 10% (17/165) of SABRIL patients experienced fatigue compared to 7% (7/104) of placebo patients. No SABRIL patients discontinued from clinical trials due to somnolence or fatigue.

Peripheral Neuropathy

SABRIL causes symptoms of peripheral neuropathy in adults. Pediatric clinical trials were not designed to assess symptoms of peripheral neuropathy, but observed incidence of symptoms based on pooled data from controlled pediatric studies appeared similar for pediatric patients on vigabatrin and placebo. In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo-controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of these signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

Weight Gain

SABRIL causes weight gain in adult and pediatric patients.

Data pooled from randomized controlled trials in adults found that 17% (77/443) of SABRIL patients versus 8% (22/275) of placebo patients gained $\geq 7\%$ of baseline body weight. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients.

Data pooled from randomized controlled trials in pediatric patients with refractory complex partial seizures found that 47% (77/163) of SABRIL patients versus 19% (19/102) of placebo patients gained $\geq 7\%$ of baseline body weight.

In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

Edema

SABRIL causes edema in adults. Pediatric clinical trials were not designed to assess edema, but observed incidence of edema based pooled data from controlled pediatric studies appeared similar for pediatric patients on vigabatrin and placebo.

Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. In adults, there was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the prescribing information: Vision Loss [see **BOXED WARNING and Warnings and Precautions**], Magnetic Resonance Imaging (MRI) Abnormalities in Infants [see **Warnings and Precautions**], Neurotoxicity [see **Warnings and Precautions**], Suicidal Behavior and Ideation [see **Warnings and Precautions**], Withdrawal of Antiepileptic Drugs (AEDs) [see **Warnings and Precautions**], Anemia [see **Warnings and Precautions**], Somnolence and Fatigue [see **Warnings and Precautions**], Peripheral Neuropathy [see **Warnings and Precautions**], Weight Gain [see **Warnings and Precautions**], Edema [see **Warnings and Precautions**].

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.

Adverse Reactions in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 4,079 SABRIL treated patients, the most commonly observed ($\geq 5\%$) adverse reactions associated with the use of SABRIL in combination with other AEDs were headache, somnolence, fatigue, dizziness, convulsion, nasopharyngitis, weight increased, upper respiratory tract infection, visual field defect, depression, tremor, nystagmus, nausea, diarrhea, memory impairment, insomnia, irritability, coordination abnormal, vision blurred, diplopia, vomiting, influenza, pyrexia, and rash.

The adverse reactions most commonly associated with SABRIL treatment discontinuation in $\geq 1\%$ of patients were convulsion and depression.

In patients with infantile spasms, the adverse reactions most commonly associated with SABRIL treatment discontinuation in $\geq 1\%$ of patients were infections, status epilepticus, developmental coordination disorder, dystonia, hypotonia, hypertonia, weight increased, and insomnia.

Most Common Adverse Reactions in Controlled Clinical Trials

Refractory Complex Partial Seizures

Adults

The following listing provides the incidence of treatment emergent adverse reactions from 2 U.S. add-on clinical studies of refractory CPS in adults.

Treatment Emergent Adverse Reactions Occurring in $\geq 2\%$ and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025).

Adverse reactions are listed by body system with the percentage (%) incidence of SABRIL 3000 mg/day (N=134) and 6000 mg/day (N=43) followed by placebo (N=135): **Ear Disorders:** tinnitus (2, 0, 1), vertigo (2, 5, 1); **Eye Disorders:** vision blurred (13, 16, 5), diplopia (7, 16, 3), asthenopia (2, 2, 0), eye pain (0, 5, 0); **Gastrointestinal Disorders:** diarrhoea (10, 16, 7), nausea (10, 2, 8), vomiting (7, 9, 6), constipation (8, 5, 3), abdominal pain upper (5, 5, 1), dyspepsia (4, 5, 3), stomach discomfort (4, 2, 1), abdominal pain (3, 2, 1), toothache (2, 5, 2), abdominal distension (2, 0, 1); **General Disorders:** fatigue (23, 40, 16), gait disturbance (6, 12, 7), asthenia (5, 7, 1), oedema peripheral (5, 7, 1), fever (4, 7, 3), chest pain (1, 5, 1), thirst (2, 0, 0), malaise (0, 5, 0); **Infections:** nasopharyngitis (14, 9, 10), upper respiratory tract infection (7, 9, 6), influenza (5, 7, 4), urinary tract infection (4, 5, 0), bronchitis (0, 5, 1); **Injury:** contusion (3, 5, 2), joint sprain (1, 2, 1), muscle strain (1, 2, 1), wound secretion (0, 2, 0); **Metabolism and Nutrition Disorders:** increased appetite (1, 5, 1), weight increased (6, 14, 3); **Musculoskeletal Disorders:** arthralgia (10, 5, 3), back pain (4, 7, 2), pain in extremity (6, 2, 4), myalgia (3, 5, 1), muscle twitching (1, 9, 1), muscle spasms (3, 0, 1); **Nervous System Disorders:** headache (33, 26, 31), somnolence (22, 26, 13), dizziness (24, 26, 17), nystagmus (13, 19, 9), tremor (15, 16, 8), memory impairment (7, 16, 3), coordination abnormal (7, 16, 2), disturbance in attention (9, 0, 1), sensory disturbance (4, 7, 2), hyporeflexia (4, 5, 1), paraesthesia (7, 2, 1), lethargy (4, 7, 2), hyperreflexia (4, 2, 3), hypoaesthesia (4, 5, 1), sedation (4, 0, 0), status epilepticus (2, 5, 0), dysarthria (2, 2, 1), postictal state (2, 0, 1), sensory loss (0, 5, 0); **Psychiatric Disorders:** irritability (7, 23, 7), depression (6, 14, 3), confusional state (4, 14, 1), anxiety (4, 0, 3), depressed mood (5, 0, 1), thinking abnormal (3, 7, 0), abnormal behaviour (3, 5, 1), expressive language disorder (1, 7, 1), nervousness (2, 5, 2), abnormal dreams (1, 5, 1); **Reproductive System:** dysmenorrhoea (9, 5, 3), erectile dysfunction (0, 5, 0); **Respiratory and Thoracic Disorders:** pharyngolaryngeal pain (7, 14, 5), cough (2, 14, 7), pulmonary congestion (0, 5, 1), sinus headache (6, 2, 1); **Skin and Subcutaneous Tissue Disorders:** rash (4, 5, 4).

Pediatrics 10 to 16 years of age

The following listing provides adverse reactions from controlled clinical studies of pediatric patients receiving SABRIL or placebo as add-on therapy for refractory complex partial seizures. The median SABRIL dose was 49.4 mg/kg (range of 8.0 – 105.9 mg/kg).

Treatment-Emergent Adverse Reactions Reported by $\geq 2\%$ of Pediatric CPS Patients (10 to 16 years of age) Treated with SABRIL and Higher than Placebo.

Adverse reactions are listed by body system with the percentage (%) incidence of SABRIL (N=109) followed by placebo (N=46): **Eye Disorders:** diplopia (5, 0), vision blurred (3, 0); **Gastrointestinal Disorders:** diarrhoea (6, 2), abdominal pain upper (3, 0), constipation (3, 2); **General Disorders:** fatigue (9, 4); **Infections and Infestations:** upper respiratory tract infection (10, 4), influenza (6, 2), otitis media (6, 2); **Investigations:** weight increased (17, 2); **Nervous System Disorders:** somnolence (6, 2), tremor (6, 0), nystagmus (5, 2), psychomotor hyperactivity (4, 2); **Psychiatric Disorders:** abnormal behavior (6, 2), aggression (5, 0), disorientation (4, 0); **Reproduction and Breast Disorders:** dysmenorrhea (3, 0); **Skin and Subcutaneous Tissue Disorders:** acne (3, 0).

Infantile Spasms

In a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by $>5\%$ of patients receiving SABRIL and that occurred more frequently than in placebo patients, were somnolence (SABRIL 45%, placebo 30%), bronchitis (SABRIL 30%, placebo 15%), ear infection (SABRIL 10%, placebo 5%), and otitis media acute (SABRIL 10%, placebo 0%).

In a dose response study of low-dose (18-36 mg/kg/day) versus high-dose (100-148 mg/kg/day) vigabatrin, no clear correlation between dose and incidence of adverse events was observed. The treatment emergent adverse reactions from the dose response study are summarized in the following listing.

Treatment-Emergent Adverse Reactions Occurring in $\geq 5\%$ of Infantile Spasms Patients.

Adverse reactions are listed by body system with the percentage (%) incidence of low-dose SABRIL (N=114) followed by high-dose SABRIL (N=108): **Eye Disorders (other than field or acuity changes):** strabismus (5, 5), conjunctivitis (5, 2); **Gastrointestinal Disorders:** vomiting (14, 20), constipation (14, 12), diarrhea (13, 12); **General Disorders:** fever (29, 19); **Infections:** upper respiratory tract infection (51, 46), otitis media (44, 30), viral infection (20, 19), pneumonia (13, 11), candidiasis (8, 3), ear infection (7, 14), gastroenteritis viral (6, 5), sinusitis (5, 9), urinary tract infection (5, 6), influenza (5, 3), group infectious (5, 1); **Metabolism & Nutrition Disorders:** decreased appetite (9, 7); **Nervous System Disorders:** sedation (19, 17), somnolence (17, 19), status epilepticus (6, 4), lethargy (5, 7), convulsion (4, 7), hypotonia (4, 6); **Psychiatric Disorders:** irritability (16, 23), insomnia (10, 12); **Respiratory Disorders:** nasal congestion (13, 4), cough (3, 8); **Skin and Subcutaneous Tissue Disorders:** rash (8, 11).

Post Marketing Experience

The following adverse reactions have been reported during post-approval use of SABRIL worldwide. All adverse reactions that are not listed above as adverse reactions reported in clinical trials, that are not relatively common in the population and are not too vague to be useful, are listed in this section. 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.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes. **Ear Disorders:** Deafness. **Endocrine Disorders:** Delayed puberty. **Gastrointestinal Disorders:** Gastrointestinal hemorrhage, esophagitis. **General Disorders:** Developmental delay, facial edema, malignant hyperthermia, multi-organ failure. **Hepatobiliary Disorders:** Cholestasis. **Nervous System Disorders:** Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis, dyskinesia. **Psychiatric Disorders:** Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder. **Respiratory Disorders:** Laryngeal edema, pulmonary embolism, respiratory failure, stridor. **Skin and Subcutaneous Tissue Disorders:** Angioedema, maculo-papular rash, pruritus, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).

DRUG INTERACTIONS

Antiepileptic Drugs

Phenytoin

Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated, since SABRIL may cause a moderate reduction in total phenytoin plasma levels [see *Clinical Pharmacology in full PI*].

Clonazepam

SABRIL may moderately increase the C_{max} of clonazepam resulting in an increase of clonazepam-associated adverse reactions [see *Clinical Pharmacology in full PI*].

Other AEDs

There are no clinically significant pharmacokinetic interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin [see *Clinical Pharmacology in full PI*].

Oral Contraceptives

SABRIL is unlikely to affect the efficacy of steroid oral contraceptives [see *Clinical Pharmacology in full PI*].

Drug-Laboratory Test Interactions

SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoaciduria).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations in full PI*].

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL 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. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Nursing Mothers

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants, 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 [see *Warnings and Precautions*].

Pediatric Use

The safety and effectiveness of SABRIL as adjunctive treatment of refractory complex partial seizures in pediatric patients aged 10 to 16 years of age have been established [see *Clinical Studies in full PI*]. The dosing recommendation in this population varies according to age group and is weight based [see *Dosage and Administration in full PI*]. Adverse reactions in this pediatric population are similar to those observed in the adult population [see *Adverse Reactions*].

The safety and effectiveness of SABRIL have not been established in pediatric patients under 10 years of age with refractory complex partial seizures.

The safety and effectiveness of SABRIL as monotherapy for pediatric patients with infantile spasms (1 month to 2 years of age) have been established [see *Dosage and Administration and Clinical Studies in full PI*].

Duration of therapy for infantile spasms was evaluated in a post hoc analysis of a Canadian Pediatric Epilepsy Network (CPEN) study of developmental outcomes in infantile spasms patients. This analysis suggests that a total duration of 6 months of vigabatrin therapy is adequate for the treatment of infantile spasms. However, prescribers must use their clinical judgment as to the most appropriate duration of use [see *Clinical Studies in full PI*].

Abnormal MRI signal changes were observed in infants [see *Warnings and Precautions*].

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Geriatric Use

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration

should be considered. Such patients may respond to a lower maintenance dose [see *Clinical Pharmacology and Dosage and Administration in full PI*].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Renal Impairment

Dose adjustment, including initiating treatment with a lower dose, is necessary in pediatric patients 10 years of age and older and adults with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see *Clinical Pharmacology and Dosage and Administration in full PI*].

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Vigabatrin is not a controlled substance.

Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see *Warnings and Precautions*].

OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical trials and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

Management of Overdosage

There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patient.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

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October 2013
VGB-L-00003

AAN Guideline Provides Recommendations for Diagnosing Rare Forms of Muscular Dystrophy

The AAN guideline may help physicians recognize various subtypes of the disease and provide proper care.

A new guideline from the American Academy of Neurology (AAN) and the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) provides recommendations about how physicians should evaluate a patient to determine which genetic tests may best diagnose his or her subtype of limb-girdle or distal muscular dystrophy. Factors to consider include symptoms, family history, ethnicity, physical examination, and laboratory test results, according to the guideline, which was published in the October 14, 2014, issue of *Neurology*.

To develop the guideline, researchers reviewed all of the available studies on the disorders, which cause muscles to waste away. “These are rare muscle diseases that can be difficult to diagnose,” said lead author Pushpa Narayanaswami, MB, Assistant Professor of Neurology at Harvard Medical School in Boston and a fellow of the AAN and AANEM. “With an accurate diagnosis, unnecessary tests or treatments may be avoided. Knowing the specific subtype is important for getting the best possible care.”

Clinical Features May Aid Diagnosis

Certain clinical features and other information such as family history can help doctors determine a person’s subtype. “Looking at a range of clinical signs and symptoms—such as which muscles are weak and if there is muscle wasting or enlargement, winging out of the shoulder blades, early signs of contracted limbs, rigidity of the neck or back, or heart or lung involvement—can help doctors determine which genetic test to order,” said senior author Anthony A. Amato, MD, Professor of Neurology at Harvard Medical School and a fellow of the AAN and AANEM. “This [technique], in turn, can shorten the time to diagnosis and start of treatment while helping avoid more extensive and expensive testing.”

Clinicians should refer newly diagnosed patients with a subtype of limb-girdle muscular dystrophy and high risk of cardiac complications for cardiology evaluation, even if they are asymptomatic, according to the guideline. Although no cure for these disorders is available, patients and physicians can manage their complications. The guideline makes recommendations about treating and managing complications, which may include muscle symptoms, heart problems, and breathing problems.

A Role for Specialized Treatment Centers

“Before this publication, there were no care guidelines that covered both limb-girdle muscular dystrophy and distal muscular dystrophy and were based on the evidence,” said Julie Bolen, PhD, MPH, Team Lead and Epidemiologist at the National Center on Birth Defects and Developmental Disabilities within the Centers for Disease Control and Prevention in Atlanta. “We hope that this guideline will fill that gap for both the people who live with these rare disorders and the health care professionals who treat them.”

The guideline recommends that care for people with these disorders be coordinated through treatment centers specializing in muscular dystrophy. People with these disorders should tell their doctors about any symptoms such as tachycardia, premature heartbeats, shortness of breath, pain, or difficulty in swallowing, according to the authors. Treatments for these symptoms may be available. People should also talk to their doctors about exercises that are safe.

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Bright Spotty Lesions May Indicate Neuromyelitis Optica Spectrum Disorder



Jae-Won Hyun, MD

The lesions may not be present among patients with multiple sclerosis or idiopathic transverse myelitis.

BOSTON—Bright spotty lesions on MRI can help neurologists distinguish neuromyelitis optica spectrum disorder (NMOSD) from other neurologic disorders, according to data presented at the 2014 Joint ACTRIMS–ECTRIMS Meeting. These lesions may be an additional MRI indicator of NMOSD, combined with aquaporin 4 antibody, which has modest sensitivity, and longitudinally extensive transverse myelitis, which is characteristic of but not a pathognomonic feature of NMOSD.

A Series of 127 MRIs

To examine the potential relationship between bright spotty lesions and NMOSD, Jae-Won Hyun, MD, a neurologist at Research Institute and Hospital of National Cancer

with signal intensities at least as high as, but not higher than, that of the surrounding CSF on a T2-weighted image without flow void effects, and not as low as that of the surrounding CSF on a T1-weighted image.

The male-to-female ratio, the mean age at attack onset, and the mean age at time of MRI were higher among people with idiopathic transverse myelitis than in participants with NMOSD and those with MS. All patients with NMOSD tested positive for aquaporin 4 antibodies. Participants with MS and those with idiopathic transverse myelitis were negative for aquaporin 4 antibodies following repeated assays using three different methods. All subjects with idiopathic transverse myelitis were negative for anti-myelin oligodendrocyte glycoprotein antibody as well.

Results suggest that bright spotty lesions are in a transient state during the acute phase of myelitis and later undergo a fundamental change in their properties.

Center in Goyang, South Korea, and colleagues analyzed 127 spinal MRIs of patients who were having an acute myelitis attack. The study was led by Ho Jin Kim, MD, PhD, Head of the MS Clinic at Research Institute and Hospital of National Cancer Center. Of the participants, 62 had NMOSD, 32 had multiple sclerosis (MS), and 33 had idiopathic transverse myelitis. One neuroradiologist and two neurologists without knowledge of the patients' diagnoses reviewed the spinal MRIs independently. The investigators defined bright spotty lesions as hyperintense spotty lesions

The Lesions' Clinical Relevance Is Uncertain

The researchers found bright spotty lesions exclusively in patients with NMOSD. Of the 62 patients with NMOSD, 17 had bright spotty lesions. Dr. Hyun and colleagues identified longitudinally extensive transverse myelitis in all study participants. MRI features, including bright spotty lesions, were completely different between patients with NMOSD and those with MS. Bright spotty lesions, however, were the only MRI feature that distinguished NMOSD from idiopathic transverse myelitis.

Among patients with NMOSD, demographic data were not significantly different between individuals with and without bright spotty lesions. The investigators thus could not draw conclusions about the bright spotty lesions' clinical relevance. To determine whether the lesions indicated attack severity, the researchers estimated the Expanded Disability Status Scale score of 36 patients with first myelitis attacks, as well as disease duration and attack numbers for all patients with NMOSD. Again, the researchers found

Bright Spotty Lesions May Indicate Neuromyelitis Optica Spectrum Disorder

continued

no significant differences between patients with NMOSD with and without lesions. The investigators concluded that bright spotty lesions could not represent attack severity. In addition, other MRI findings were not significantly different between the two groups.

Dr. Hyun and colleagues followed up the patients with bright spotty lesions longitudinally. They performed 14 follow-up MRIs at two to 20 months after baseline.

No bright spotty lesions were detectable on follow-up MRI, but high signal intensities on T2 images remained for some patients. The results suggest that bright spotty

lesions exist in a transient state during the acute phase of myelitis and ultimately undergo a fundamental change in properties, like contrast-enhanced lesions do, said Dr. Hyun.

—Erik Greb

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**Approximately 50% of individuals
with narcolepsy are undiagnosed.¹**



**TIRED
ALL THE TIME**

**CATAPLEXY
HYPNAGOGIC
HALLUCINATIONS
EXCESSIVE DAYTIME
SLEEPINESS
SLEEP
PARALYSIS
SLEEP
DISRUPTION**

**Narcolepsy symptoms may be
lurking beneath the surface.**

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To identify the symptoms of narcolepsy, **LOOK DEEPER**

C

Cataplexy: A sudden, temporary loss of muscle tone triggered by strong emotions^{1,2}

H

Hypnagogic Hallucinations: Vivid dream-like experiences that occur during the transitions between wake and sleep^{1,2}

E

Excessive Daytime Sleepiness: The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep²

S

Sleep Paralysis: The temporary inability to move or speak while falling asleep or waking up²

S

Sleep Disruption: The interruption of sleep by frequent awakenings^{1,2}

C.H.E.S.S. is a useful mnemonic for recalling the 5 symptoms of narcolepsy,³ although not all patients experience all symptoms.² Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy.² All patients with narcolepsy have excessive daytime sleepiness.² The presence of cataplexy is pathognomonic for narcolepsy.²

Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder^{2,3}

Narcolepsy is a chronic, life-disrupting neurologic disorder in which the brain is unable to regulate sleep-wake cycles normally, resulting in sleep-wake state instability.¹⁻⁴

Narcolepsy Is Underdiagnosed

It is estimated that approximately 50% or more of individuals with narcolepsy remain undiagnosed.¹ Initial onset of symptoms typically occurs between the ages of 15-25,² although an accurate diagnosis can take more than 10 years.¹

Narcolepsy Symptoms Can Be Difficult to Recognize

Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.^{1,2} The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.^{1,2,5} Individual symptoms should be evaluated carefully to determine whether they are due to narcolepsy or another condition. Looking deeper at the symptoms can help healthcare professionals establish a differential diagnosis.

Get a Deeper Look, at www.NarcolepsyLink.com

Narcolepsy Link contains resources to help identify narcolepsy symptoms and facilitate communications with your patients.



ALS Onset Occurs Earlier in Non-Caucasians

The earlier age of disease onset among non-Caucasians, compared with Caucasians, was also consistent between men and women.

BALTIMORE—The age of disease onset in patients with amyotrophic lateral sclerosis (ALS) is significantly earlier in non-Caucasians than in Caucasians, according to research presented at the 139th Annual Meeting of the American Neurological Association. In non-Caucasians, the mean age at onset of ALS is 55.6, compared with a mean age of 61.4 among Caucasians.

It is unclear whether the earlier age of disease onset results from a biological phenomenon or is a consequence of socioeconomic factors, commented Hristelina Ilieva, MD, PhD. “Comparison of comorbidities, neurologic and non-neurologic, may help us further understand this finding,” she added. Dr. Ilieva is a neurology resident at the Methodist Neurological Institute in Houston.

Studies have found increasing evidence of ethnic variation in the incidence of motor neuron diseases. For example, Asians have the lowest reported incidence, while the incidence is intermediate in African populations, mixed in Central and South American populations, and highest in Caucasians. Prior research has also found significant differences between Caucasians and African Americans in the age of disease onset and in disease course.

Dr. Ilieva and Ericka Simpson, MD, Director, Neurology Residency Program and Neuromuscular Medicine Fellowship Program at the Methodist Neurological Institute, conducted a retrospective review based on a database of all patients who were evaluated and diagnosed with definite or probable ALS. The patients were grouped into two categories—373 Caucasians and 86 non-Caucasians, which included Asians, Hispanics, and African Americans.

The researchers compared the age of disease onset, time to diagnosis, initial BMI, site of disease onset, disease progression, and early disease course between the two groups of participants. In addition, the investigators compared ALS Functional Rating Scale–Revised scores for the subgroup of patients who had three consecutive visits. Disease

progression was measured using the Appel ALS score. Statistical analyses were performed using two-tailed *t*-test.

Among non-Caucasians, the mean age of disease onset was 55.4 in males and 55.7 in females. In Caucasians, the mean age of disease onset was 60.2 in males and 62.9 in females. Overall, the time to diagnosis in non-Caucasians was 19.6 months, compared with 16.3 months in Caucasians.

Mean ALS onset age is 61.4 in Caucasians and 55.6 in non-Caucasians.

“We confirmed prior observations that non-Caucasian patients’ age of disease onset is significantly earlier than in Caucasian patients,” said Dr. Ilieva. “This observation was consistent between genders as well. Unlike earlier reports, we were unable to find a difference in disease course between the two groups. Our results may be affected by the dropout of patients seen in follow-up.”

Previous studies also had found that non-Caucasians may present with more advanced disease at their initial visit. “We calculated preslope and delta factor of safety to address this possibility and were unable to confirm this observation in our cohort,” Dr. Ilieva commented.

—Colby Stong

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New Tests May Accurately Detect Creutzfeldt–Jakob Disease

One test analyzes epithelial samples obtained from nasal brushings, and the other examines urine samples.

Two minimally invasive assays for detecting prions that are diagnostic of Creutzfeldt–Jakob disease (CJD) in living patients show promise, according to preliminary studies published August 7, 2014, in the *New England Journal of Medicine*.

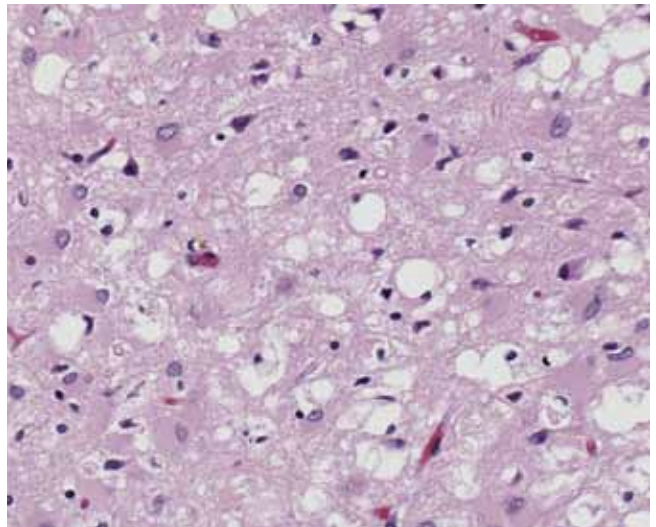
One assay tests epithelial samples obtained from nasal brushings, and the other tests urine samples. Both tests can be used in patients suspected of having the sporadic, inherited, or acquired forms of CJD, such as variant CJD and iatrogenic CJD. Both assays had sensitivities and specificities ranging between 93% and 100% in small patient populations in these exploratory studies. This range of sensitivities and specificities is better than the diagnostic accuracy of CSF testing.

If these findings are replicated in larger studies, both assays will have the potential for establishing a definitive diagnosis of CJD in clinical settings. The test that uses nasal brushings may establish a definitive diagnosis earlier in the course of the disease than has been possible previously, thus potentially enabling intervention for this fatal neurodegenerative disorder.

In addition, the incidental finding that simple brushing of the olfactory mucosa yields a greater quantity of prion seeds than is found in CSF suggests that infectivity may be present in the nasal cavity, which has important biosafety implications, the researchers noted.

Epithelial Test Had 100% Specificity

In the first report, investigators applied real-time quaking-induced conversion technology to olfactory epithelium samples from 31 patients who had rapidly progressive dementia and were referred for evaluation of possible or probable CJD. These patients concurrently underwent CSF sampling. Twelve patients with other neurodegenerative disorders, primarily Alzheimer's disease or Parkinson's disease, and 31 patients who had no neurologic disorders were controls, said Christina D. Orrú, PhD, a researcher at the Laboratory of Persistent Viral Diseases at the National



Both assays can be used in patients suspected of having the sporadic, inherited, or acquired forms of Creutzfeldt–Jakob disease (CJD), such as variant CJD and iatrogenic CJD.

Institute of Allergy and Infectious Diseases's Rocky Mountain Laboratories in Hamilton, Montana, and her colleagues.

Obtaining the nasal brushings was described as a gentle procedure in which unседated patients were first given a local vasoconstrictor applied with a nasal tampon, and then had a fiber-optic rhinoscope with a disposable sheath inserted into the nasal cavity to locate the olfactory mucosal lining of the nasal vault. A sterile, disposable brush was inserted alongside the rhinoscope, gently rolled on the mucosal surface, withdrawn, and immersed in saline solution in a centrifuge tube for further preparation.

The assays using this material yielded positive results for all 15 patients who had definite sporadic CJD, 13 of the 14 who had probable sporadic CJD, and both patients who had inherited CJD. In contrast, all 43 controls had negative results. This performance represents a sensitivity of 97% and a specificity of 100% in this study popula-

New Tests May Accurately Detect Creutzfeldt–Jakob Disease

continued

tion. In comparison, testing of CSF samples from the same patients had a 77% sensitivity, said Dr. Orrú and her associates.

The substantial prion seeding in the olfactory mucosa, which was of greater magnitude than that in the CSF, raises the possibility that CJD prions could contaminate patients' nasal discharges. "Nasal and aerosol-borne transmission of prion diseases have been documented in animal models, but there is no epidemiologic evidence for aerosol-borne transmission of sporadic CJD" to date, the investigators wrote.

Medical instruments that come into contact with the nasal mucosa may become contaminated with prions, "which poses the question of whether iatrogenic transmission is possible. Therefore, further study of possible biohazards ... is warranted," the authors concluded.

Urine Test Was Highly Sensitive

In the second study, Fabio Moda, PhD, then a postdoctoral fellow at the Mitchell Center for Research in Alzheimer's Disease and Related Brain Disorders at the University of Texas in Houston, and his associates assayed urine samples for minute quantities of the misfolded prion protein using an extensive amplification technology. The group tested samples from 68 patients with sporadic CJD, 14 with variant CJD, and 156 controls. The control group included four patients with genetic prion diseases, 50 with other neurodegenerative disorders (eg, Alzheimer's disease, Parkinson's disease, frontotemporal dementia, motor neuron disease, and progressive supranuclear palsy), 50 patients with nondegenerative neurologic disorders (chiefly cerebrovascular disease, multiple sclerosis, epilepsy, brain tumors, autoimmune encephalitis, and meningitis), and 52 healthy adults.

This assay had a sensitivity of 93% and a specificity of 100% in distinguishing CJD from other brain disorders and from brain health in this patient population, said the authors. The quantities of the prion protein excreted in

the urine were extremely small, so the researchers did not address the potential for infectivity in this study.

Better Specificity Estimates Are Needed

These findings are encouraging because clinicians and researchers have long sought a sensitive and minimally invasive diagnostic tool specifically targeted to the protein that causes all forms of CJD, said Colin L. Masters, MD, Deputy Director of Mental Health at the Florey Institute of Neuroscience and Mental Health, University of Melbourne, in an accompanying editorial.

It will be important for additional studies to determine more precise estimates of the tests' specificities, which are necessitated by the wide confidence intervals reported, because the tests can lead to breakthrough false-positive results.

CJD "is extremely uncommon, and a test without near-perfect specificity may also result in many false positive results if it is applied to patients with a low probability of having the disease," said Dr. Masters. "In these circumstances, it is important to highlight the preliminary nature of these studies."

Moreover, the finding that abnormal prion protein seeds are found in the olfactory mucosa "at concentrations equivalent to those in diseased brain, and several logs greater than those in CSF," has implications for infection control. "Some experts have [already] recommended appropriate decontamination of surgical instruments that come into contact with the olfactory epithelium of patients at high risk for CJD," he concluded.

—Mary Ann Moon

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VNS May Benefit Children With Dravet Syndrome

The treatment may reduce disabling seizures among children whose epilepsy is refractory to medication.



Stephen P. Fulton, MD

SEATTLE—Vagal nerve stimulation (VNS) decreases the number of disabling seizures and increases alertness in children with Dravet syndrome, according to a retrospective analysis presented at the 68th Annual Meeting of the American Epilepsy Society. The treatment thus may benefit children whose seizures have failed to respond to several anticonvulsants and the ketogenic diet.

“The absence of neurocognitive side effects and drug interactions makes VNS an attractive treatment option, particularly for children with Dravet syndrome, who often have additional comorbidities,” said Stephen P. Fulton, MD, Assistant Professor of Pediatrics and Neurology at the University of Tennessee Health Science Center in Memphis. “VNS should be offered early on to children with Dravet syndrome and refractory seizures.”

Dr. Fulton and colleagues reviewed outpatient clinic and inpatient hospital records from their institution for the period from January 2005 to December 2012 to identify patients with Dravet syndrome who had had VNS implantation. The investigators examined the patients’ charts to identify their type of epilepsy, age at the time of seizure onset, seizure types, seizure frequency, medications used, response to VNS, and complications related to surgery or device replacement. Patients whose battery was approaching the end of its service were offered generator reimplantation if the family and doctor thought that the patients were benefiting from VNS. If the patient was not thought to be benefiting from VNS and the family requested removal of the device, the device was explanted after the battery was exhausted.

The researchers identified 12 patients whose VNS was implanted at their institution. Nine of these patients had at least 50% reduction in generalized tonic-clonic seizures. Two patients became seizure-free at one year after implantation. Four of the nine patients who achieved seizure reduction of at least 50% reported significant cognitive and speech improvements within six months of implantation.

The two patients who became seizure-free at one year had been on a rapid-cycling treatment regimen (ie, 7 s on and 0.2 or 0.3 min off) with output currents of 1.75 mA and 2 mA, respectively. Of the nine patients with seizure reduction of at least 50%, five used rapid cycling exclusively, one used intermediate cycling (ie, 30 s on and 1.8 or 3 min off) exclusively, two changed from rapid to intermediate cycling, and one changed from rapid to standard cycling (ie, 30s on and 5 min off) five years after implantation.

Three patients did not have marked improvement in their seizures. One of these children had improvement in absence seizures but worsening of generalized tonic-clonic seizures. One child had no improvement and no worsening. The third patient had significant improvement in seizure control but worsened behavioral difficulties.

—Erik Greb

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Could Parkinson's Disease Shed Light on Multiple System Atrophy?

Symptomatic and pathologic similarities could help investigators direct research into a rare and fatal disorder.

LAS VEGAS—Significant commonalities between multiple system atrophy (MSA) and Parkinson's disease suggest that knowledge about the latter disorder could help direct research into the former, according to an overview provided at the recent Global MSA Research Roadmap Meeting. But despite their neuropathologic and symptomatic similarities, MSA and Parkinson's disease are notably different diseases, researchers said.

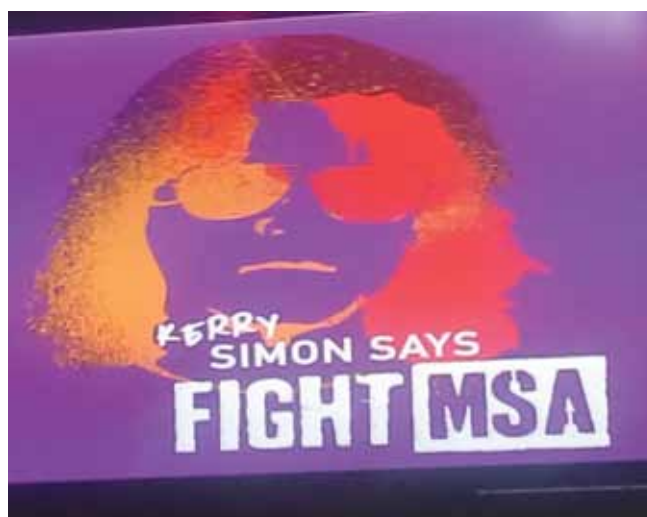
MSA is a rare but fatal adult-onset neurodegenerative disorder of uncertain etiology. It is characterized by features such as autonomic failure and parkinsonism and, like Parkinson's disease, is marked by the deposition of abnormally phosphorylated α -synuclein.

Biomarkers and Therapeutic Targets

Of all of the features of Parkinson's disease, the pathogenic cascade may have the most potential for guiding future research into MSA, said Patrik Brundin, MD, PhD, Director of the Center for Neurodegenerative Science at the Van Andel Research Institute in Grand Rapids, Michigan. Although the primary aspects of pathogenesis distinguish the two diseases, the latter share several secondary phenomena such as proinflammatory mechanisms. These phenomena could be useful in the development of biomarkers and therapeutic targets. Knowledge about the pathogenic cascade in Parkinson's disease, however, is limited.

"We don't really understand Parkinson's disease pathogenesis," said Dr. Brundin. "We are painfully ignorant ... We still don't really know what causes the cell death and the degeneration. But we can ask the question, 'Is it likely to be similar to MSA?'"

Research by Jellinger, Kuzdas-Wood, and others has prompted investigators to propose a five-part pathogenic cascade for MSA. The cascade begins with the healthy



Despite their neuropathologic and symptomatic similarities, multiple system atrophy and Parkinson's disease are notably different diseases.

neuron and glial cell until the oligodendrocytes "get sick," which results in neuronal degeneration, said Dr. Brundin. The next part encompasses α -synuclein accumulation in the oligodendroglial cytoplasm, followed by "failure of mitochondrial function, loss of trophic factor support, possible loss of proteosomal function, and increased oxidative stress." In the following step, oligodendroglia degenerate, and the final phase involves secondary neuronal loss accompanied by microglial and astroglial activation.

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Do you have patients diagnosed with Multiple System Atrophy?

Multiple System Atrophy (MSA) is a rare, sporadic, progressive, neurodegenerative disorder of the central and autonomic nervous systems. Although the etiology of MSA is unknown, the generation of cytotoxic oxidants by the enzyme myeloperoxidase (MPO) may play an important role in the disease process. AstraZeneca plans to conduct a Phase 2 clinical trial with AZD3241, a potent, selective, brain-permeable MPO inhibitor. The study, entitled “*A 12-Week, Multicenter, Randomized, Parallel-Group Study to Assess the Safety, Tolerability, Pharmacokinetics, Biomarker Effects, Efficacy, and Effect on Microglia Activation, as Measured by Positron Emission Tomography, of AZD3241 in Subjects with Multiple System Atrophy*” is anticipated to start in the first half of this year. The study is double-blind and placebo-controlled, and will investigate two dosage levels of AZD3241. The study will be conducted at sites in the United States and Europe. Future studies are planned, including a study of longer duration focusing on safety and efficacy.

The primary objectives of this study are:

- To assess the safety and tolerability of AZD3241 in patients with MSA.
- To determine the effect of AZD3241 on microglia activation, as measured by PET imaging of [¹¹C]PBR28 binding at baseline and after 12 weeks of treatment (2 scans per patient), in patients with MSA.

A secondary objective is:

- To determine the biomarker effects of AZD3241 in patients with MSA.

Exploratory objectives are:

- To assess the pharmacokinetics of AZD3241 in patients with MSA.
- To assess the efficacy of AZD3241 in patients with MSA. Exploratory efficacy outcome measures include the Unified Multiple System Atrophy Rating Scale (UMSARS), the Composite Autonomic Symptom Scale (COMPASS) Select Change Scale (CCS), and the MSA–Quality of Life scale (MSA-QoL).

Patients may qualify for the study if they:

- Are 30-80 years old.
- Meet criteria for diagnosis of possible or probable MSA (parkinsonian- or cerebellar-subtype) according to the consensus criteria.
- Do not have significant neurological disease other than MSA that may affect motor or autonomic function.

Potential patient eligibility will be confirmed by an independent clinical expert. A Data and Safety Monitoring Board (DSMB) will monitor unblinded safety data on an ongoing basis to ensure the continuing safety of patients.

The study involves:

- A participation period of approximately five months for each patient
- Twelve weeks of treatment with study medication
- Approximately twelve study visits, including two visits to one of five global PET centers
- Imaging procedures, including the use of a radioligand
- Physical and neurological examinations
- Blood draws, ECGs, and vital signs assessments
- Administration of questionnaires

Patients may be compensated for their time and/or travel.



If you'd like more information on this study, or other studies with AZD3241, please contact Alicia Savage, Project Director, at alicia.savage@azneuro.com using “[AZD3241 Neurology Reviews](#)” in the subject line.

Could Parkinson's Disease Shed Light on Multiple System Atrophy?

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Several factors have been implicated in Parkinson's disease, but researchers are uncertain about which ones are important, said Dr. Brundin. Krismer et al enumerated distinguishing and overlapping features of MSA and Parkinson's disease. The pathogenic element that distinguishes MSA from Parkinson's disease is the oligodendrocyte pathology, "possibly this p25 alpha transportation to membrane, and then, as a secondary event, the neurons dying," said Dr. Brundin. Parkinson's disease probably starts with synaptic pathology and proceeds with retrograde degeneration toward the cell body, he added.

Treatment options for MSA are limited and mainly provide symptomatic relief. No therapies modify the disease. The development of new biomarkers could enable

Although α -synuclein misfolding does not occur in the same way in Parkinson's disease and MSA, the diseases share enough similarities to make the process one of the more important things that researchers who study MSA have learned from Parkinson's disease

earlier diagnosis and allow treatment to begin at symptom onset, which is when disease severity is lower. "We desperately need biomarkers," said Dr. Brundin.

Potential biomarkers include α -synuclein imaging and MRI morphometry; neuroinflammation imaging; and blood, plasma, and CSF biomarkers for inflammation, α -synuclein, and other proteins.

Knowledge about Parkinson's disease may be of little help in the development of disease-modifying therapies for MSA, said Dr. Brundin. "Considering that there is still no drug that's been proven to slow the progression of Parkinson's disease, how on Earth are we going to be able to use any information from that field of research in MSA? Hopefully, in the future there will be a drug that slows the progression of Parkinson's disease."

The strategy of targeting extracellular α -synuclein and emerging data on neuroinflammation in Parkinson's disease could be relevant to MSA research. "If we get a drug that enhances mitochondrial function ... perhaps it can be used in MSA," said Dr. Brundin. Glial cell line-derived neurotrophic factor, which has been tested with limited success in Parkinson's disease, might be a better therapy for MSA, he added.

Protein Handling or Misfolding

Although α -synuclein misfolding does not occur in the same way in Parkinson's disease and MSA, the diseases share enough similarities to make the process one of the more important things that researchers who study MSA have learned from Parkinson's disease, said Ronald Melki, PhD, Director of Research at the Laboratoire d'Enzymologie et Biochimie Structurales of the Centre National de la Recherche Scientifique in Gif-sur-Yvette, France.

The misfolding process begins when newly synthesized proteins unfold in cells or are degraded incorrectly. This occurrence populates folding intermediates that assemble in fibrillar aggregates, which are the hallmark of various neurodegenerative diseases. Primary neurons take up fibrillar α -synuclein and transport it through the axon, and second-order neurons ultimately internalize it, explained Dr. Melki. "This [process] suggests that these aggregates are propagating within our brain in a manner reminiscent of prion protein propagation."

One unanswered question with implications for future research is whether Parkinson's disease and MSA are the consequences of distinct strains of α -synuclein. "I have a tendency ... to answer 'yes' because we have one protein [that is] assembled into two different forms that have two different molecular codes," said Dr. Melki. Electron microscopy shows that one form of the protein resembles spaghetti and the other resembles linguine. "These two fibrils are getting a different sort of pathology or different distribution in the brain. So, we think that we have strains that are distinct structurally and functionally—exactly what people have described ... in the prion field."

Investigators must use methods developed for prion research, such as amplification of protein assemblies from patients through sonication, added Dr. Melki. In a recent study conducted with colleagues from Bordeaux,

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Symptomatic neurogenic orthostatic hypotension (NOH) is caused by disorders such as primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), which can be associated with norepinephrine deficiency.^{1,2}

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NORTHERA™ (droxidopa) is a norepinephrine prodrug³ and is the first medication approved for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic NOH caused by primary autonomic failure (PD, MSA, and PAF), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of NORTHERA should be assessed periodically.

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IMPORTANT SAFETY INFORMATION

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA.

CONTRAINDICATIONS

- None.

WARNINGS AND PRECAUTIONS

- **Supine Hypertension:** NORTHERA therapy may cause or exacerbate supine hypertension in patients with NOH, which may increase cardiovascular risk if not well-managed.
- **Hyperpyrexia and Confusion:** Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in Japan with NORTHERA use. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.
- **Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure:** NORTHERA therapy may exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure.

- **Allergic Reactions:** This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

- The most common adverse reactions (greater than 5%) were headache, dizziness, nausea, hypertension, and fatigue.

DRUG INTERACTIONS

- Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension. Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.

USE IN SPECIFIC POPULATIONS

- Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited. There are no adequate and well-controlled trials of NORTHERA in pregnant women. Women who are nursing should choose nursing or NORTHERA. The safety and effectiveness of NORTHERA in pediatric patients have not been established. No overall differences in safety or effectiveness were observed between subjects aged 75 years and older and younger subjects in clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

Visit NORTHERA.com to download a treatment form, or call the NORTHERA Support Center at 844-601-0101

Please see Brief Summary on the following page and full Prescribing Information, including Boxed Warning, at www.NORTHERA.com.



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NORTHERA™ (droxidopa) capsules, for oral use**Brief Summary of Prescribing Information**(See package insert for full Prescribing Information or visit www.Northera.com)**Rx Only****WARNING: SUPINE HYPERTENSION**

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA [see *Warnings and Precautions*].

INDICATIONS AND USAGE – NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure [Parkinson’s disease (PD), multiple system atrophy, and pure autonomic failure], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been established. The continued effectiveness of NORTHERA should be assessed periodically.

CONTRAINDICATIONS – None.

WARNINGS AND PRECAUTIONS – Supine Hypertension: NORTHERA therapy may cause or exacerbate supine hypertension in patients with NOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Monitor blood pressure, both in the supine position and in the recommended head-elevated sleeping position. Reduce or discontinue NORTHERA if supine hypertension persists. If supine hypertension is not well-managed, NORTHERA may increase the risk of cardiovascular events.

Hyperpyrexia and Confusion: Post-marketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with NORTHERA use during post-marketing surveillance in Japan. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.

Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure: NORTHERA may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Careful consideration should be given to this potential risk prior to initiating therapy in patients with these conditions.

Allergic Reactions: This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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 clinical practice. The safety evaluation of NORTHERA is based on two placebo-controlled studies 1 to 2 weeks in duration (Studies 301 and 302), one 8-week placebo-controlled study (Study 306), and two long-term, open-label extension studies (Studies 303 and 304). In the placebo-controlled studies, a total of 485 patients with Parkinson’s disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy were randomized and treated, 245 with NORTHERA and 240 with placebo [see *Clinical Studies*].

Placebo-Controlled Experience: The most commonly observed adverse reactions (those occurring at an incidence of greater than 5% in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group) in NORTHERA-treated patients during the three placebo-controlled trials were headache, dizziness, nausea, hypertension. The most common adverse reactions leading to discontinuation from NORTHERA were hypertension or increased blood pressure and nausea.

Table 1. Most Common Adverse Reactions Occurring More Frequently in the NORTHERA Group

	Study 301 and Study 302 (1 to 2 Weeks Randomized Treatment)		Study 306 (8 to 10 Weeks Randomized Treatment)	
	Placebo (N=132) n (%)	NORTHERA (N=131) n (%)	Placebo (N=108) n (%)	NORTHERA (N=114) n (%)
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)

Note: n=number of patients. Table displays adverse reactions that were reported in greater than 5% of patients in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group.

Long-Term, Open-Label Trials with NORTHERA: In the long-term, open-label extension studies, a total of 422 patients, mean age 65 years, were treated with NORTHERA for a mean total exposure of approximately one year. The commonly reported adverse events were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).

DRUG INTERACTIONS – Drugs that Increase Blood Pressure: Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension. **Parkinson’s Medications:** Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.

USE IN SPECIFIC POPULATIONS – Pregnancy: Pregnancy Category C: There are no adequate and well-controlled trials in pregnant women. Following consecutive oral administration at doses of 60, 200, and 600 mg/kg/day to pregnant Sprague Dawley rats, increased incidences of lower body weight and occurrence of undulant rib were noted in fetuses, but they were slight and spontaneously reversed after birth. Based on dose per unit body surface area, these three doses correspond to approximately 0.3, 1, and 3 times, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient. Shortening of the gestation period was observed in rats at 600 mg/kg/day. Low incidences of renal lesions (cysts, indentations, or renal pelvic dilation) were observed on the surface of the kidneys of female rats treated with droxidopa during the period of fetal organogenesis. No other potentially teratogenic effects have been observed in rats or rabbits. **Nursing Mothers:** Choose nursing or NORTHERA. In rats, droxidopa is excreted in breast milk, and when the drug was administered to the nursing dams during the period of lactation, reduced weight gain and reduced survival were observed in the offspring. **Pediatric Use:** The safety and effectiveness of NORTHERA in pediatric patients have not been established. **Geriatric Use:** A total of 197 patients with symptomatic NOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and 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. **Patients with Renal Impairment:** NORTHERA and its metabolites are primarily cleared renally. Patients with mild or moderate renal impairment (GFR greater than 30 mL/min) were included in clinical trials and did not have a higher frequency of adverse reactions. Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited.

OVERDOSAGE – Symptoms: There was one case of overdose reported during post-marketing surveillance in Japan. The patient ingested 7,700 mg of NORTHERA and experienced a hypertensive crisis that resolved promptly with treatment. **Treatment:** There is no known antidote for NORTHERA overdose. In case of an overdose that may result in an excessively high blood pressure, discontinue NORTHERA and treat with appropriate symptomatic and supportive therapy. Counsel patients to remain in a standing or seated position until their blood pressure drops below an acceptable limit.

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DRX-L-00003 August 2014

Could Parkinson's Disease Shed Light on Multiple System Atrophy?

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he obtained samples from patients who developed disease and amplified the assemblies in test tubes. The process resulted in fibrils that the investigators will inject into animals to evaluate whether they reproduce the distinct diseases.

—Fred Balzac

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A Patient's Path to Narcolepsy Diagnosis Is Frequently a Long and Winding Road

More than half of patients with narcolepsy were initially misdiagnosed, and two-thirds of patients were evaluated by multiple physicians.

NEW ORLEANS—The median length of time from when patients contacted a health care professional until they were diagnosed with narcolepsy was 22 months, while 44% of patients were diagnosed within one year and 18% were diagnosed more than five years after symptom onset, according to research presented at the 2013 Annual Meeting of the American Neurological Association.

About 67% of patients were evaluated by multiple physicians before being diagnosed with narcolepsy. In addition, 85% of patients were rated as having moderate to severe symptoms at their initial visit, and these symptoms often interfered with daytime functioning, reported Christine Acebo, PhD, Medical Scientist at Jazz Pharmaceuticals in Palo Alto, California, and colleagues.

“Even though many of these patients had pathologic hypersomnia and other characteristic symptoms of narcolepsy as well as health insurance, [the patients] often had remarkably long and variable paths to receiving a diagnosis of narcolepsy,” stated Dr. Acebo, who is also an Adjunct Assistant Professor of Psychiatry and Human Behavior at the Warren Alpert Medical School of Brown University in Providence, Rhode Island.

Journey to a Narcolepsy Diagnosis

The researchers conducted a physician survey and chart review to analyze how patients ultimately were diagnosed with narcolepsy. A total of 77 physicians in neurology, pulmonology, psychiatry, and other areas reviewed 252 patient charts for the survey. About 55% of patients were men (median age, 38), and 67% were white. At least half of the patients were obese, and two-thirds had a comorbid disorder, with psychiatric and metabolic comorbidities the most frequent.

According to the researchers, 67% of patients were referred to the respondent physician by another physician or health care provider, and 76% were referred by their primary care physician. The respondent physician diagnosed narcolepsy in 72% of cases in which a patient was referred; in 28% of referrals, the

referring provider had made the diagnosis. The most common reason for referral was excessive daytime sleepiness (occurring in 87% of such cases), followed by trouble staying awake during the day (in 39%).

The most common symptom at initial presentation was excessive daytime sleepiness, occurring in 90% of patients; more than 40% had trouble staying awake or functioning during the day, and 26% had difficulties with activities of daily living. About 85% of patients were rated as having moderate or severe symptoms at their initial visit, with more than one-third having severe symptoms.

A High Rate of Misdiagnosis

The investigators reported that misdiagnoses occurred in 60% of patients. The most common misdiagnoses were depression (31%), insomnia (20%), and obstructive sleep apnea (13%). About 67% of participants had been observed by multiple providers before being diagnosed with narcolepsy.

Dr. Acebo stated that “even among the physicians who made the diagnosis, patients were frequently seen multiple times—only 51% were diagnosed by the respondent physician at the first visit. Many patients experienced a substantial delay from their report of the onset of their symptoms to receiving a diagnosis of narcolepsy.”

“The presence of comorbid conditions, some with symptoms overlapping with narcolepsy, likely increased the complexity of making a diagnosis and resulted in more than 50% of patients being misdiagnosed prior to receiving a narcolepsy diagnosis,” the investigators concluded. “Taken together, these data highlight the need for increased awareness and timely diagnosis of the signs and symptoms of narcolepsy.”

—Colby Stong

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New Daily Persistent Headache Is Often Associated With a Precipitating Event



Robert P. Cowan, MD

Headache specialists ask whether the disease may be better understood as a secondary headache disorder.

LOS ANGELES—Most cases of new daily persistent headache (NDPH) are associated with a precipitating event such as a flu-like or viral illness, according to research presented at the 56th Annual Scientific Meeting of the American Headache Society. The study results are consistent with other research that identified flu-like or viral illness and upper respiratory infection as the most common precipitants of NDPH.

“Given this association, the question arises whether NDPH should be more properly classified as a secondary headache disorder similar to post-traumatic headache,” said Robert P. Cowan, MD, Clinical Professor of Neurology and Neurological Sciences at Stanford Hospital and

majority of patients (62%) had migrainous features such as photophobia (46%) or phonophobia (46%). About 38% of patients had nausea. In addition, 58% of patients had pressure-like pain similar to that of tension-type headache.

Nearly all patients (92%) had a normal neurologic exam. Approximately 56% of patients had a family history of headache, and 24% had a history of migraine or primary headache disorder. About three-quarters of patients associated an inciting event with the onset of their headache. The inciting event was a preceding infection for 45% of patients, recent surgery for 24% of patients, psychologic stress for 10% of patients, trauma for 7% of patients, and other inciting event for 14%.

“Our data suggest that NDPH is an uncommon diagnosis, even in the quaternary headache center setting,” said Dr. Cowan. “Of the 3,579 patients seen by the Stanford Headache Clinic since its opening in July 2011, only 35 (1%) met diagnostic criteria for NDPH ... and 78 (2%) met criteria for post-traumatic headache, while 2,604 (73%) had a diagnosis of migraine, with the remainder of patients having other primary and secondary headache disorders.”

—Erik Greb

A flu-like or viral illness may precede new daily persistent headache.

Clinics in California. “Further research is needed to better understand the underlying mechanism of NDPH to guide more effective treatment options.”

Dr. Cowan and colleagues searched Stanford’s medical records for patients admitted between January 2005 and January 2014 with NDPH. The researchers found 85 individuals coded with NDPH, 38 of whom met the diagnostic criteria in the 2013 International Classification of Headache Disorders III (beta). The team reviewed these patients’ charts in detail.

Approximately 53% of patients with NDPH were male, 55% were Caucasian, and 8% were Asian. The

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For more information about Xenazine, please see Brief Summary of Prescribing Information on adjacent pages.

XENAZINE® (tetrabenazine) Tablets

Indications and Usage:

XENAZINE is indicated for the treatment of chorea associated with Huntington's disease.

Important Safety Information:

WARNING: DEPRESSION AND SUICIDALITY

See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease.
 - Balance risks of depression and suicidality with the clinical need for control of choreiform movements when considering the use of XENAZINE.
 - Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior.
 - Inform patients, caregivers, and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician.
 - Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation.
 - XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.
- XENAZINE is also contraindicated in patients who have impaired hepatic function or are taking monoamine oxidase inhibitors (MAOIs) or reserpine. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. At least 20 days should elapse after stopping reserpine before starting XENAZINE.
- Prescribers should periodically re-evaluate the need for XENAZINE in their patients by assessing the beneficial effect on chorea and possible adverse effects including worsening mood, cognition, rigidity, and functional capacity. XENAZINE should be titrated slowly over several weeks for a dose that is appropriate for each patient.
- Before a dose greater than 50 mg is administered, the patient's CYP2D6 metabolizer status should be determined. Do not exceed 50 mg/day or 25 mg/dose if XENAZINE is administered with a strong CYP2D6 inhibitor.
- XENAZINE therapy should be retitrated if there is a treatment interruption of greater than 5 days, or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications.

- A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with XENAZINE. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The management of NMS should include immediate discontinuation of XENAZINE and other drugs not essential to concurrent therapy.
- XENAZINE can also cause other serious side effects including: akathisia, restlessness, agitation, parkinsonism, and sedation/somnolence. These side effects may require a dose reduction or discontinuation of XENAZINE. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension. Dysphagia has also been reported with use of XENAZINE; some cases of dysphagia were associated with aspiration pneumonia.
- QT prolongation-related arrhythmias have been reported with use of XENAZINE. XENAZINE should not be used in combination with drugs known to prolong QTc (which in certain circumstances can lead to torsades de pointes and/or sudden death), in patients with congenital long QT syndrome, or in patients with a history of cardiac arrhythmias. A potentially irreversible syndrome of involuntary, dyskinetic movements called tardive dyskinesia (TD) may develop in patients treated with neuroleptic drugs. If signs and symptoms of TD appear in a patient treated with XENAZINE, drug discontinuation should be considered. Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.
- XENAZINE elevates serum prolactin concentrations. XENAZINE may induce sedation/somnolence which may impair the ability to drive or operate dangerous machinery. Alcohol or other sedating drugs can worsen sedation/somnolence.
- Some adverse events such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism, and akathisia may be dose-dependent. If the adverse effect does not resolve or decrease, consideration should be given to lowering or discontinuing XENAZINE. The most commonly reported adverse events with XENAZINE compared to placebo were sedation/somnolence (31% vs 3%), fatigue (22% vs 13%), insomnia (22% vs 0%), depression (19% vs 0%), akathisia (19% vs 0%), anxiety (15% vs 3%), and nausea (13% vs 7%).

For more information, please see the full Prescribing Information, including Boxed Warning, the Medication Guide, or go to www.XenazineUSA.com.

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Xenazine® (tetrabenazine) Tablet, for Oral Use
Brief Summary of Prescribing Information

(See package insert for full Prescribing Information or visit www.XenazineUSA.com)

INDICATIONS AND USAGE

XENAZINE is indicated for the treatment of chorea associated with Huntington's disease.

WARNING: DEPRESSION AND SUICIDALITY

See full prescribing information for complete boxed warning.

- **Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease.**
- **Balance risks of depression and suicidality with the clinical need for control of choreiform movements when considering the use of XENAZINE.**
- **Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior.**
- **Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician.**
- **Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation.**
- **XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.**

DOSAGE AND ADMINISTRATION

General Dosing Considerations

The chronic daily dose of XENAZINE used to treat chorea associated with Huntington's disease (HD) is determined individually for each patient. When first prescribed, XENAZINE therapy should be titrated slowly over several weeks to identify a dose of XENAZINE that reduces chorea and is tolerated. XENAZINE can be administered without regard to food.

Individualization of Dose

The dose of XENAZINE should be individualized.

Dosing Recommendations Up to 50 mg per day

The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. XENAZINE should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If a dose of 37.5 to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. If adverse events such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

Dosing Recommendations Above 50 mg per day

Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs.

Extensive and Intermediate CYP2D6 Metabolizers

Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse events such as akathisia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

Poor CYP2D6 Metabolizers

In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg.

CYP2D6 Inhibitors

Strong CYP2D6 Inhibitors

Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., fluoxetine, paroxetine) significantly increase the exposure to α -HTBZ and β -HTBZ, therefore, the total dose of XENAZINE should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg.

Patients with Hepatic Impairment

Because the safety and efficacy of the increased exposure to XENAZINE and other circulating metabolites are unknown, it is not possible to adjust the dosage of XENAZINE in hepatic impairment to ensure safe use. Therefore, XENAZINE is contraindicated in patients with hepatic impairment.

Discontinuation of Treatment

Treatment with XENAZINE can be discontinued without tapering. Re-emergence of chorea may occur within 12 to 18 hours after the last dose of XENAZINE.

Resumption of Treatment

Following treatment interruption of greater than five (5) days, XENAZINE therapy should be re-titrated when resumed. For short-term treatment interruption of less than five (5) days, treatment can be resumed at the previous maintenance dose without titration.

CONTRAINDICATIONS

XENAZINE is contraindicated in patients who are actively suicidal, or in patients with untreated or inadequately treated depression. XENAZINE is contraindicated in patients with impaired hepatic function. XENAZINE is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. XENAZINE is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Adverse Effects

Huntington's disease is a progressive disorder characterized by changes in mood, cognition,

chorea, rigidity, and functional capacity over time. In a 12-week controlled trial, XENAZINE was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is unknown. Therefore, proper use of the drug requires attention to all facets of the underlying disease process over time.

Prescribers should periodically re-evaluate the need for XENAZINE in their patients by assessing the beneficial effect on chorea and possible adverse effects, including depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness and disability. It may be difficult to distinguish between drug-induced side-effects and progression of the underlying disease; decreasing the dose or stopping the drug may help the clinician distinguish between the two possibilities. In some patients, underlying chorea itself may improve over time, decreasing the need for XENAZINE.

Dosing of XENAZINE

Proper dosing of XENAZINE involves titration of therapy to determine an individualized dose for each patient. When first prescribed, XENAZINE therapy should be titrated slowly over several weeks to allow the identification of a dose that both reduces chorea and is tolerated. Some adverse effects such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism and akathisia may be dose-dependent and may resolve or lessen with dosage adjustment or specific treatment. If the adverse effect does not resolve or decrease, consider discontinuing XENAZINE.

Doses above 50 mg should not be given without CYP2D6 genotyping patients to determine if they are poor metabolizers.

Risk of Depression and Suicidality

Patients with Huntington's disease are at increased risk for depression, suicidal ideation or behaviors (suicidality). XENAZINE increases the risk for suicidality in patients with HD. All patients treated with XENAZINE should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with XENAZINE.

In a 12-week, double-blind placebo-controlled study in patients with chorea associated with Huntington's disease, 10 of 54 patients (19%) treated with XENAZINE were reported to have an adverse event of depression or worsening depression compared to none of the 30 placebo-treated patients. In two open-label studies (in one study, 29 patients received XENAZINE for up to 48 weeks; in the second study, 75 patients received XENAZINE for up to 80 weeks), the rate of depression/worsening depression was 35%.

In all of the HD chorea studies of XENAZINE (n=187), one patient committed suicide, one attempted suicide, and six had suicidal ideation.

Clinicians should be alert to the heightened risk of suicide in patients with Huntington's disease regardless of depression indices. Reported rates of completed suicide among individuals with Huntington's disease range from 3-13% and over 25% of patients attempt suicide at some point in their illness.

Patients, their caregivers, and families should be informed of the risks of depression, worsening depression, and suicidality associated with XENAZINE and should be instructed to report behaviors of concern promptly to the treating physician. Patients with HD who express suicidal ideation should be evaluated immediately.

Laboratory Tests

Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE.

Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α -HTBZ and 9-fold for β -HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg.

Risk of Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with XENAZINE and other drugs that reduce dopaminergic transmission. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection), and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of XENAZINE and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

Recurrence of NMS has been reported. If treatment with XENAZINE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Risk of Akathisia, Restlessness, and Agitation

In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, akathisia was observed in 10 (19%) of XENAZINE-treated patients and 0% of placebo-treated patients. In an 80-week open-label study, akathisia was observed in 20% of XENAZINE-treated patients. Akathisia was not observed in a 48-week open-label study. Patients receiving XENAZINE should be monitored for the presence of akathisia. Patients receiving XENAZINE should also be monitored for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia, the XENAZINE dose should be reduced; however, some patients may require discontinuation of therapy.

Risk of Parkinsonism

XENAZINE can cause parkinsonism. In a 12-week double-blind, placebo-controlled study in patients with chorea associated with HD, symptoms suggestive of parkinsonism (i.e., bradykinesia, hypertonía and rigidity) were observed in 15% of XENAZINE-treated patients compared to 0% of placebo-treated patients. In 48-week and 80-week open-label studies, symptoms suggestive of parkinsonism were observed in 10% and 3% of XENAZINE-treated patients, respectively. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between this drug-induced side-effect and progression of the underlying disease process. Drug-induced parkinsonism has the

potential to cause more functional disability than untreated chorea for some patients with Huntington's disease. If a patient develops parkinsonism during treatment with XENAZINE, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.

Risk of Dysphagia

Dysphagia is a component of HD. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia may be associated with aspiration pneumonia. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, dysphagia was observed in 4% of XENAZINE-treated patients and 3% of placebo-treated patients. In 48-week and 80-week open-label studies, dysphagia was observed in 10% and 8% of XENAZINE-treated patients, respectively. Some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

Risk of Sedation and Somnolence

Sedation is the most common dose-limiting adverse effect of XENAZINE. In a 12-week, double-blind, placebo-controlled trial in patients with chorea associated with HD, sedation/somnolence was observed in 17/54 (31%) XENAZINE-treated patients and in 1 (3%) placebo-treated patient. Sedation was the reason upward titration of XENAZINE was stopped and/or the dose of XENAZINE was decreased in 15/54 (28%) patients. In all but one case, decreasing the dose of XENAZINE resulted in decreased sedation. In 48-week and 80-week open-label studies, sedation/somnolence was observed in 17% and 57% of XENAZINE-treated patients, respectively. In some patients, sedation occurred at doses that were lower than recommended doses.

Patients should not perform activities requiring mental alertness to maintain the safety of themselves or others, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of XENAZINE and know how the drug affects them.

Interaction with Alcohol

Patients should be advised that the concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Risk of QTc Prolongation

XENAZINE causes a small increase (about 8 msec) in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. The use of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.

XENAZINE should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Concomitant Use of Neuroleptic Drugs, Reserpine and MAOIs

Neuroleptic Drugs: Patients taking neuroleptic (antipsychotic) drugs (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone) were excluded from clinical studies during the XENAZINE development program. Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists. **Reserpine:** Reserpine binds irreversibly to VMAT2, and the duration of its effect is several days. The physician should wait for chorea to reemerge before administering XENAZINE to avoid overdosage and major depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting XENAZINE. XENAZINE and reserpine should not be used concomitantly. **Monoamine Oxidase Inhibitors (MAOIs):** XENAZINE is contraindicated in patients taking MAOIs. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.

Risk of Hypotension and Orthostatic Hypotension

XENAZINE induced postural dizziness in healthy volunteers receiving single doses of 25 or 50 mg. One subject had syncope and one subject with postural dizziness had documented orthostasis. Dizziness occurred in 4% of XENAZINE-treated patients (vs. none on placebo) in the 12-week controlled trial; however, blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

Risk of Hyperprolactinemia

XENAZINE elevates serum prolactin concentrations in humans. Following administration of 25 mg to healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if XENAZINE is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecomastia and impotence can be caused by elevated serum prolactin concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown. Chronic increase in serum prolactin levels (although not evaluated in the XENAZINE development program) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of XENAZINE.

Risk of Tardive Dyskinesia (TD)

A potentially irreversible syndrome of involuntary, dyskinesic movements may develop in patients treated with neuroleptic drugs. In an animal model of orofacial dyskinesias, acute administration of reserpine, a monoamine depletor, has been shown to produce vacuous chewing in rats. Although the pathophysiology of tardive dyskinesia remains incompletely understood, the most commonly accepted hypothesis of the mechanism is that prolonged post-synaptic dopamine receptor blockade leads to supersensitivity to dopamine. Neither reserpine nor XENAZINE, which are dopamine depletors, have been reported to cause clear tardive dyskinesia in humans, but as pre-synaptic dopamine depletion could theoretically lead to supersensitivity to dopamine, and XENAZINE can cause the extrapyramidal symptoms also known to be associated with neuroleptics (e.g., parkinsonism and akathisia), physicians should be aware of the possible risk of tardive dyskinesia. If signs and symptoms of TD appear in a patient treated with XENAZINE, drug discontinuation should be considered.

Use in Patients with Concomitant Illnesses

Clinical experience with XENAZINE in patients with systemic illnesses is limited.

Depression and Suicidality

XENAZINE may increase the risk for depression or suicidality in patients with a history of depression or suicidal behavior or in patients with diseases, conditions, or treatments that cause depression or suicidality. XENAZINE is contraindicated in patients with untreated or inadequately treated depression or who are actively suicidal.

Hepatic Disease

XENAZINE is contraindicated in patients with hepatic impairment.

Heart Disease

XENAZINE has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials.

Binding to Melanin-Containing Tissues

Since XENAZINE or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that XENAZINE may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of the eye was conducted in the chronic toxicity study in dogs. Ophthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure.

The clinical relevance of XENAZINE's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions in Controlled Clinical Trials

The most common adverse reactions from Table 1 occurring in over 10% of XENAZINE-treated patients, and at least 5% greater than placebo, were sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (19%), akathisia (19%), and nausea (13%).

Clinical Studies 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, XENAZINE was administered to 773 unique subjects and patients. The conditions and duration of exposure to XENAZINE varied greatly, and included single and multiple dose clinical pharmacology studies in healthy volunteers (n=259) and open-label (n=529) and double-blind studies (n=84) in patients.

In a randomized, 12-week, placebo-controlled clinical trial of HD subjects, adverse reactions (ARs) were more common in the XENAZINE group than in the placebo group. Forty-nine of 54 (91%) patients who received XENAZINE experienced one or more ARs at any time during the study. The ARs most commonly reported (over 10%, and at least 5% greater than placebo) were sedation/somnolence (31% vs. 3% on placebo), fatigue (22% vs. 13% on placebo), insomnia (22% vs. 0% on placebo), depression (19% vs. 0% on placebo), akathisia (19% vs. 0% on placebo), and nausea (13% vs. 7% on placebo).

Adverse Reactions Occurring in ≥4% Patients

The number and percentage of the most commonly reported AEs that occurred at any time during the study in ≥4% of XENAZINE-treated patients, and with a greater frequency than in placebo-treated patients, are presented in Table 1 in decreasing order of frequency within body systems for the XENAZINE group.

Table 1. Treatment Emergent Adverse Reactions in Patients Treated with XENAZINE and with a Greater Frequency than Placebo in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

Body System	AE Term	XENAZINE n = 54 n (%)	Placebo n = 30 n (%)
PSYCHIATRIC DISORDERS	Sedation/somnolence	17 (31%)	1 (3%)
	Insomnia	12 (22%)	-
	Depression	10 (19%)	-
	Anxiety/anxiety aggravated	8 (15%)	1 (3%)
	Irritability	5 (9%)	1 (3%)
	Appetite decreased	2 (4%)	-
CENTRAL & PERIPHERAL NERVOUS SYSTEM	Obsessive reaction	2 (4%)	-
	Akathisia	10 (19%)	-
	Balance difficulty	5 (9%)	-
	Parkinsonism/bradykinesia	5 (9%)	-
	Dizziness	2 (4%)	-
	Dysarthria	2 (4%)	-
	Gait unsteady	2 (4%)	-
	Headache	2 (4%)	1 (3%)
GASTROINTESTINAL SYSTEM DISORDERS	Nausea	7 (13%)	2 (7%)
	Vomiting	3 (6%)	1 (3%)
BODY AS A WHOLE – GENERAL	Fatigue	12 (22%)	4 (13%)
	Fall	8 (15%)	4 (13%)
	Laceration (head)	3 (6%)	-
	Ecchymosis	3 (6%)	-
RESPIRATORY SYSTEM DISORDERS	Upper respiratory tract infection	6 (11%)	2 (7%)
	Shortness of breath	2 (4%)	-
	Bronchitis	2 (4%)	-
URINARY SYSTEM DISORDERS	Dysuria	2 (4%)	-

Dose escalation was discontinued or dosage of study drug was reduced because of one or more ARs in 28 of 54 (52%) patients randomized to XENAZINE. These ARs consisted of sedation (15), akathisia (7), parkinsonism (4), depression (3), anxiety (2), fatigue (1) and diarrhea (1). Some patients had more than one AR and are, therefore, counted more than once.

Adverse Reactions Due to Extrapyramidal Symptoms (EPS)

The following table describes the incidence of events considered to be extrapyramidal adverse reactions.

Table 2. Treatment Emergent EPS in Patients Treated with XENAZINE Occurring with a Greater Frequency than Placebo in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

Event	Patients (%) reporting event	
	XENAZINE n = 54	Placebo n = 30
Akathisia ¹	10 (19%)	0
Extrapyramidal event ²	8 (15%)	0
Any extrapyramidal event	18 (33%)	0

¹Patients with the following adverse event preferred terms were counted in this category: akathisia, hyperkinesia, restlessness.

²Patients with the following adverse event preferred terms were counted in this category: bradykinesia, parkinsonism, extrapyramidal disorder, hypertonía.

Patients may have had events in more than one category.

Laboratory Tests

No clinically significant changes in laboratory parameters were reported in clinical trials with XENAZINE. In controlled clinical trials, XENAZINE caused a small mean increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), laboratory values as compared to placebo.

Vital Signs

In controlled clinical trials, XENAZINE did not affect blood pressure, pulse, and body weight. Orthostatic blood pressure was not consistently measured in the XENAZINE clinical trials.

DRUG INTERACTIONS

Strong CYP2D6 Inhibitors

In vitro studies indicate that α -HTBZ and β -HTBZ are substrates for CYP2D6. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to these metabolites. A reduction in XENAZINE dose may be necessary when adding a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine) in patients maintained on a stable dose of XENAZINE. The daily dose of XENAZINE should not exceed 50 mg per day and the maximum single dose of XENAZINE should not exceed 25 mg in patients taking strong CYP2D6 inhibitors.

Reserpine

Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea to reemerge before administering XENAZINE to avoid overdosage and major depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting XENAZINE. XENAZINE and reserpine should not be used concomitantly.

Monoamine Oxidase Inhibitors (MAOIs)

XENAZINE is contraindicated in patients taking MAOIs. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.

Alcohol

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Drugs that Cause QTc Prolongation

Since XENAZINE causes a small increase in QTc prolongation (about 8 msec), the concomitant use with other drugs that are known to cause QTc prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval. XENAZINE should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Neuroleptic Drugs

Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. XENAZINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Tetrabenazine had no clear effects on embryo-fetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m² basis). Tetrabenazine had no effects on embryo-fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m² basis). Because neither rat nor rabbit dosed with tetrabenazine produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately addressed the potential effects of tetrabenazine on embryo-fetal development in humans. When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m² basis. Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, this study may not have adequately assessed the potential effects of tetrabenazine on the offspring of women exposed *in utero* and via lactation.

Labor and Delivery

The effect of XENAZINE on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether XENAZINE or its metabolites are excreted in human milk. Since many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from XENAZINE, a decision should be made whether to discontinue nursing or to discontinue XENAZINE, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of XENAZINE in children have not been established.

Geriatric Use

The pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied in geriatric subjects.

Use in Patients with Hepatic Disease

The use of XENAZINE in patients with liver disease is contraindicated.

Use in Patients with Depression and Suicidality

Patients with HD are at increased risk for depression, suicidal ideation and behavior (suicidality), and XENAZINE increases these risks. XENAZINE is contraindicated in patients with untreated or inadequately treated depression or who are actively suicidal. XENAZINE may increase the risk for depression or suicidality in patients with a history of depression or suicidal behavior or in patients with diseases, conditions, or treatments that cause depression or suicidality.

Depression

Symptoms of sadness, worsening of depression, withdrawal, insomnia, irritability, hostility (aggressiveness), akathisia (psychomotor restlessness), anxiety, agitation, or panic attacks may increase with XENAZINE. Depression/worsening depression was noted in 35% of XENAZINE-treated patients during studies with XENAZINE.

Suicidality

The rate of completed suicide among individuals with Huntington's disease ranges from 3-13% and over 25% of patients with HD attempt suicide at some point in their illness.

Use in Poor or Extensive CYP2D6 Metabolizers

Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers (EMs).

Poor Metabolizers

Poor CYP2D6 metabolizers (PMs) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α -HTBZ and 9-fold for β -HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient's CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs.

Extensive/Intermediate Metabolizers

In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg.

Use in Patients at Risk from QTc Prolongation

XENAZINE causes a small increase in QTc interval (8 msec). It should be avoided in patients with congenital long QT syndrome, or a history of hypokalemia or hypomagnesemia, or cardiac arrhythmias (e.g., bradycardia), or in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol), antiarrhythmic medications or any other medications known to prolong the QTc interval.

Use in Patients with Renal Disease

The effects of renal insufficiency in the pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

XENAZINE is not a controlled substance.

Abuse

Clinical trials did not reveal any tendency for drug seeking behavior, though these observations were not systematic. Abuse has not been reported from the postmarketing experience in countries where XENAZINE has been marketed.

As with any CNS-active drug, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of XENAZINE misuse or abuse (such as development of tolerance, increasing dose requirements, drug-seeking behavior).

Abrupt discontinuation of XENAZINE from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re-emerge.

OVERDOSAGE

Human Experience

Three episodes of overdose occurred in the open-label trials performed in support of registration. Eight cases of overdose with XENAZINE have been reported in the literature. The dose of XENAZINE in these patients ranged from 100 mg to 1g. Adverse reactions associated with XENAZINE overdose included acute dystonia, oculogyric crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, rubor, and tremor.

Management of Overdose

Treatment should consist of those general measures employed in the management of overdose with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR®).

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XZN455



Deerfield, IL 60015, U.S.A.

Surgery May Reduce Seizure Frequency in Patients With Lennox–Gastaut Syndrome

Children with a one-sided brain abnormality may be candidates for curative epilepsy surgery.

SEATTLE—Resective epilepsy surgery may be an effective treatment option for certain children with Lennox–Gastaut syndrome secondary to early focal brain lesion or injury, according to findings presented at the 68th Annual Meeting of the American Epilepsy Society.

Ahsan Moosa Naduvil, MD, a neurologist at the Cleveland Clinic Epilepsy Center, and colleagues studied 36 patients with Lennox–Gastaut syndrome who underwent epilepsy surgery at the Cleveland Clinic for focal, lobar, or multilobar resection or hemispherectomy between June 1, 2002 and June 31, 2012.

All participants had developed epilepsy as a result of brain lesions or injuries. Of the 36 patients, 17 sustained injury before they were born, 10 sustained injury immediately before or after they were born, and nine sustained

When the investigators conducted follow-up visits at six months to 6.6 years after surgery, they observed that 19 patients were seizure-free. Of the patients who still were having seizures, two had late remission at two years after surgery, and five became almost seizure-free, with an average of nine seizures per month. At the last follow-up visit, 24 patients were either seizure-free or had experienced a major reduction in seizure frequency.

“In the past, children with features of Lennox–Gastaut syndrome were not considered to be candidates for epilepsy surgery that involves removal of the seizure focus,” said Dr. Naduvil. “Our study confirms that selected children with early brain lesions may be rendered seizure-free with epilepsy surgery.”

The authors performed a survival analysis based on the duration of time between seizures. They calculated the chance of seizure freedom as 60.1% at 12 months, 51% at 24 months, and 40.8% at 30 months or more.

“Most of the patients with Lennox–Gastaut syndrome are not candidates for curative surgery, but there is a small subset—especially the ones with an MR abnormality, especially the ones with a one-sided brain abnormality. They may be candidates for epilepsy surgery,” said Dr. Naduvil. Before a neurologist considers palliative surgery for a patient with Lennox–Gastaut syndrome who is not responding to medications, he or she should evaluate the patient for a curative surgery, he concluded.

—Erik Greb

“Our study confirms that selected children with early brain lesions may be rendered seizure-free with epilepsy surgery.”

—Ahsan Moosa Naduvil, MD

injury between ages 2 months and 3 years. At the time of surgery, the patients ranged in age from newborn to 18 years and were experiencing multiple seizures per day.

Exploring the FDA's Flexibility With Novel Orphan Therapies



Frank J. Sasinowski,
MS, MPH, JD

The FDA has consistently exercised reasonable, appropriate, science-based flexibility in its review and approval of rare disease therapies.

ALEXANDRIA, VIRGINIA—Since the 1983 passage of the Orphan Drug Act, the FDA has approved 162 orphan drugs and new chemical entities for noncancer rare diseases. The Orphan Drug Act grants the FDA flexibility in its review of these therapies, but has the FDA actually exercised flexibility in the approval process, and if it has, what is the nature and scope of that flexibility?

At the National Organization for Rare Disorders (NORD) Rare Diseases and Orphan Products Breakthrough Summit, Frank J. Sasinowski, MS, MPH, JD, reviewed the FDA's track record with regard to the approval of novel orphan therapies. Mr. Sasinowski is a Director at Hyman, Phelps & McNamara, a food and drug law firm specializing in the areas of new drug development, controlled substances, advertising, and health care law.

"Three years ago, at this very summit, I unveiled the analysis that had been done looking at how the FDA had approved the 135 orphan drugs and new chemical entities from the time the Orphan Drug Act was enacted through July 1, 2010," Mr. Sasinowski said. "What I want to do today is present an update—what's happened in the four years since 2010."

A Bit of Background

In 1962, the food and drug laws were changed to require that the sponsor of a new drug show by substantial treatment effectiveness that a drug has a benefit. This was to be done through adequate, well-controlled studies, which was interpreted to mean two. But for rare disease therapies, that presented unique challenges. The Orphan Drug Act addressed some of these challenges but did not change the quantity of evidence that was necessary for approval.

In 1983, Mr. Sasinowski was working at the FDA. It was his original analysis of the Orphan Drug Act that led to the

1984 and 1985 amendments to the law that made it work. Of the 135 drug approvals reviewed for the original analysis, Mr. Sasinowski was personally involved in about 20%. Of the 27 approvals since the original analysis, Mr. Sasinowski was again involved in about 20%. "I know the law and I know how much evidence the FDA needs to make an approval," Mr. Sasinowski said.

For his original analysis, Mr. Sasinowski gathered all the statistical and medical reviews of the 135 new chemical entities that were approved up to July 1, 2010. "It filled 27 boxes, and I personally read 27 boxes of medical and statistical

The 1962 laws requiring the sponsor of a new drug to show by substantial treatment effectiveness that a drug has a benefit, by means of adequate, well-controlled studies, presented unique challenges for rare disease therapies.

information," he said. He then classified each approval into one of three categories.

"The first thing I did was to see whether there were two adequate, well-controlled studies that met their primary end points by their prespecified primary analysis," Mr. Sasinowski continued. "I classified those as 'conventional.' Those were not different from anything else—that is, they would have been approved if they were for hypertension. And that's all I was going to do. I was just going to say conventional or not." The 'not' category would mean regulatory flexibility.

Exploring the FDA's Flexibility With Novel Orphan Therapies

continued

But one senior FDA official, Dr. Robert Temple, suggested providing more detail. "So after I declared that an approval wasn't conventional, I then determined whether it was based on administrative flexibility," which was defined as one of those systems the FDA has in place (such as Subpart H, which is also called accelerated approval or fast track, or another formal regulatory system such as FDAMA 115), or if not approved under administrative flexibility, then the approval was classified as an example of case-by-case flexibility.

Ninety of 135 orphan drug approvals (67%) from 1983 to 2010 resulted from some exercise of FDA flexibility. "Two-thirds of all the orphans that were approved were approved with some form of flexibility. This shows that the FDA was exercising reasonable, appropriate, science-based flexibility in its review and approval of these applications," Mr. Sasinowski said. While the concept might not have been surprising, the numbers were. "It really startled people. This was a game changer." People had a vague sense that the FDA was treating orphans different, "but until I did the analysis, no one knew what that really meant—no one at FDA, no one in industry, no one in academia or in the investment community," Mr. Sasinowski said.

That Was Then, This Is Now

The original findings set the stage, but an update was needed. "We were looking to see whether that degree of flexibility that we saw in the first 27 years of the FDA's

implementation of the Orphan Drug Act was still occurring in the last four years," Mr. Sasinowski said. He and his colleagues undertook an analysis of the 27 new orphan drugs approved in the past four years (again excluding cancer therapies), and the results were exactly the same as in the

During the past four years, 19 orphan products were approved through regulatory flexibility.

original analysis. About two-thirds of the approvals for rare disease therapies involved some form of flexibility. Specifically, 19 orphan products were approved through regulatory flexibility. Most of them (14) were approved with administrative flexibility. An additional five required case-by-case flexibility. The remaining eight products that were approved met conventional evidentiary requirements.

"The FDA is maintaining the same level of flexibility, which is commendable," Mr. Sasinowski said. "The FDA continues to show the same degree of flexibility that it has since the beginning."

—Glenn S. Williams

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Could Quantitative EEG Analysis Provide a Biomarker for Huntington's Disease?



Simon P. Fisher, PhD

Increased gamma and theta activity precedes other sleep and behavioral abnormalities in a mouse model of the disease.

BALTIMORE—Early changes in quantitative EEG measures, such as increased gamma and theta activity in all sleep-wake states, may be a reliable biomarker of Huntington's disease in mice, according to research presented at the 27th Annual Meeting of the Associated Professional Sleep Societies.

"Identifying the source of the abnormal gamma oscillations in this model could tell us a lot about the pathophysiology of the disease," said Simon P. Fisher, PhD. Increased theta activity and a slowing of theta peak frequency suggest the involvement of the hippocampus, and previous investigations of the R6/2 mouse model of Huntington's disease have found inclusion bodies and polyglutamine aggregates in the hippocampus.

"Identifying the source of the abnormal gamma oscillations in this model could tell us a lot about the pathophysiology of the disease."

—Simon P. Fisher, PhD

Sleep-wake disruption and abnormalities in the EEG are evident in R6/2 mice and in humans with Huntington's disease, but neurologists cannot yet make direct translational inferences from these data, said Dr. Fisher, Research Scientist at SRI International in Menlo Park, California. Further studies of EEG changes in other pre-clinical models will be necessary to validate these findings, particularly because no single model recapitulates

all features of the human disease. Nevertheless, the present study supports the EEG as a potential biomarker in preclinical drug development for Huntington's disease, he added.

A Longitudinal Analysis of Sleep Phenotype

Dr. Fisher and colleagues conducted a longitudinal analysis of the sleep phenotype in R6/2 mice. The investigators implanted 7-week-old male and female R6/2 mice for EEG and performed 48-hour baseline recordings at 9, 13, and 17 weeks of age. During the 10-week study, the mice underwent three sleep-deprivation periods at each of these ages, each of which was followed by a recovery period. Throughout the study, the researchers recorded the mice's activity and body temperature continuously using inductive telemetry.

During the study, activity patterns for R6/2 mice disintegrated, and the mice displayed a consistent low level of activity throughout each 24-hour day by 17 weeks. In addition, the diurnal rhythm of body temperature flattened in R6/2 mice by 13 weeks and was disrupted dramatically by 17 weeks. Pronounced hypothermia during the dark period at this time suggested severe metabolic disturbances in the mouse model, said Dr. Fisher.

Gamma Activity Increased in R6/2 Mice

Gamma activity was between six and eight times greater in the non-REM sleep of R6/2 mice, compared with wild-type mice, by 17 weeks. Theta power also increased in REM and non-REM sleep for the R6/2 mice, compared with wild-type mice.

In addition, baseline non-REM delta power decreased in R6/2 mice, compared with wild-type mice.

Could Quantitative EEG Analysis Provide a Biomarker for Huntington's Disease?

continued

The investigators also examined non-REM delta power after sleep deprivation. No differences were evident between R6/2 and wild-type mice at nine weeks, but the researchers observed crested impairments in R6/2 mice at 13 weeks that progressed to 17 weeks, suggesting that the sleep rebound is compromised in these mice. Theta peak frequency also decreased progressively for R6/2 mice.

“One of the main aims of future research is to understand how these sleep abnormalities in this phenotype interact with the other symptoms in this model—particularly cognitive dysfunction and altered metabolism,” said Dr. Fisher. In previous studies, cognitive function improved

in R6/2 mice that received hypnotics and stimulants to normalize their sleep-wake cycles. This work suggests that treating sleep disorders “might be a novel therapeutic angle in Huntington's disease,” concluded Dr. Fisher.

—Erik Greb

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Tool May Help Identify Cognitive Deficits in Patients With Huntington's Disease

The brief cognitive measure may not distinguish between healthy subjects and persons at risk for the disease, however.

SAN DIEGO—The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) may help neurologists assess cognitive deficits in patients with Huntington's disease, according to a study presented at the 65th Annual Meeting of the American Academy of Neurology. Results of the RBANS correlate well with those of other common cognitive and functional measures for patients with Huntington's disease and persons at risk for the disorder. The test may be less useful, however, in distinguishing between at-risk individuals and healthy individuals, except when the at-risk individuals are estimated to be within 10 years of disease onset.

Comparing RBANS and Other Common Cognitive Tests

Elizabeth Breen, research assistant at Neurosciences University of California in San Diego, and colleagues administered the RBANS to 25 patients with Huntington's disease, 28 patients at risk for the disease, and 19 controls. The participants also underwent the Mini Mental State Examination, the Montreal Cognitive Assessment, the Mattis Dementia Rating Scale, and the Total Functional Capacity section of the Unified Huntington's Disease Rating Scale.

The researchers compared RBANS scores for each study group using a one-way analysis of variance and multiple comparisons tests. Ms. Breen also used Pearson's *r* to examine the correlation between RBANS scores and the other cognitive and functional measures.

RBANS Results Distinguished Controls From Patients With Huntington's Disease

The study participants were well matched with regard to age and education. At-risk subjects and controls had similar scores on the cognitive measures, but scores for patients with Huntington's

disease indicated cognitive impairment. At-risk subjects and controls achieved perfect scores on functional measures, and the Huntington's group's average score was 9, which indicates mild functional impairment. Patients with Huntington's disease also exhibited more motor symptoms than did at-risk individuals.

The researchers found significant differences in mean RBANS total scores and in each of the subscales between patients with Huntington's disease and controls. The effect sizes were also large. Patients with Huntington's disease "were impaired and had lower scores, [but] were nowhere near the bottom of the scale," said Ms. Breen. "On the other hand, the controls didn't really approach a maximum score in any category. This suggests that the RBANS doesn't show floor or ceiling effects," she added.

A comparison of mean RBANS scores for patients with Huntington's disease and at-risk individuals revealed significant differences in total score and in each of the subscales except the visuospatial section. Again, the effect sizes were large.

No significant differences in RBANS scores were apparent, however, between at-risk subjects and controls. When the researchers compared at-risk patients who were within 10 years of disease onset—according to the Langbehn equation—to controls, they found significant differences in total RBANS score, visuospatial ability, and delayed memory. Effect sizes in those categories were large. "This [result] suggests that as patients get closer to conversion to Huntington's disease, the RBANS might be sensitive to some of the cognitive changes that begin to appear," said Ms. Breen.

—Erik Greb

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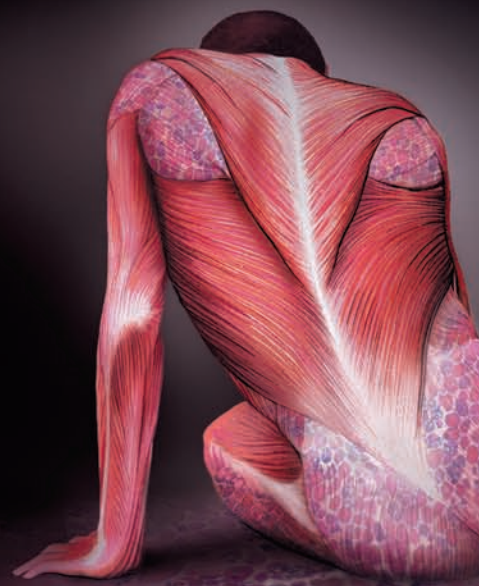
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