

The Challenges in Long-Chain Fatty Acid Oxidation Disorders: Unmet Needs of Treatment and Management

HIGHLIGHTS

- › Long-Chain Fatty Acid Oxidation Disorders and Current Management Strategies
- › Long-Chain Fatty Acid Oxidation Disorders: Managed Care and Specialty Pharmacy Implications
- › CE Sample Posttest

The Challenges in Long-Chain Fatty Acid Oxidation Disorders: Unmet Needs of Treatment and Management

Release date: August 14, 2020

Expiration date: August 14, 2021

Estimated time to complete activity: 2.0 hours

Type of activity: Application

Medium: Print with internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by an educational grant from Ultragenyx Pharmaceutical Inc.

Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances in the treatment of fatty acid oxidation disorders.

Activity Overview

Long-chain fatty acid oxidation disorders (LC-FAODs) are a group of rare and life-threatening autosomal recessive genetic diseases caused by metabolic deficiencies that prevent the body from converting long-chain fatty acids into energy. The clinical manifestations of these rare genetic disorders due to the resultant energy deficiency cause substantial morbidity and mortality. LC-FAODs significantly affect patient and caregiver quality of life. Current recommended management of LC-FAODs includes nutrition support by avoidance of fasting combined with the use of low-fat/high-carbohydrate diets, medium-chain triglyceride supplementation and in some cases, carnitine supplementation. The recent approval of the odd-chain fatty acid triheptanoin, a highly purified, pharmaceutical-grade, medium-chain triglyceride, marks the first FDA-approved therapy for this rare disease. This supplement highlights the pathophysiology and clinical findings, management strategies, and clinical trial data for the recently approved therapy and agents under investigation.

Statement of Educational Need

Fatty acid oxidation disorders (FAODs) are serious inborn errors of metabolism due to disruption of either mitochondrial β -oxidation or fatty acid transport using the carnitine transport pathway. Long-chain FAODs (LC-FAODs) are characterized by acute crises of energy metabolism and severe energy deficiency that may present with rhabdomyolysis, liver dysfunction, severe hypoglycemia, and cardiomyopathy. Although these

are rare disorders, it has been estimated that the combined incidence of LC-FAODs among the United States, Australia, and Germany is 1:9300 live births. Most cases are diagnosed via newborn screening; however, it remains that patients with these disorders may experience major clinical events and morbidity, with overall mortality rates for LC-FAODs estimated at greater than 50% over the past 3 decades. Although research is ongoing into therapies for LC-FAODs, both the clinical efficacy and cost-effectiveness of emerging agents has yet to be fully determined. Continuing education surrounding the burden and potential treatment of LC-FAODs will improve managed care professionals' and specialty pharmacists' knowledge and competency in managing patients with LC-FAODs through a greater insight into the new treatment modalities and strategies to optimize therapy and potentially improve outcomes.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Examine the pathophysiology and clinical presentation associated with the most common types of long-chain fatty acid oxidation disorders (LC-FAODs).
- Identify significant disease-related complications and the limitations of current standards of care for managing LC-FAODs that affect patient quality of life.
- Explore emerging therapy for LC-FAODs, including novel mechanism of action, safety and efficacy from clinical trials, and adverse effects.
- Illustrate the role of the managed care provider in improving patient access to novel therapies and their impact in improving patient outcomes.

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The Challenges in Long-Chain Fatty Acid Oxidation Disorders: Unmet Needs of Treatment and Management

OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge of the current management of long-chain fatty acid oxidation disorders and evaluate recently approved therapies and those under development with potential to improve outcomes in this patient population.

TABLE OF CONTENTS

Participating Faculty	Sxxx
Reports	
Long-Chain Fatty Acid Oxidation Disorders and Current Management Strategies	Sxxx
<hr/>	
<i>Jerry Vockley, MD, PhD</i>	
Long-Chain Fatty Acid Oxidation Disorders: Managed Care and Specialty Pharmacy Implications	Sxxx
<hr/>	
<i>Alan Pannier, PharmD, MBA</i>	
CE Sample Posttest	Sxxx

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EDITORIAL SUPPORT DISCLOSURES

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Long-Chain Fatty Acid Oxidation Disorders and Current Management Strategies

Jerry Vockley, MD, PhD

Introduction

The Role of Fatty Acids in Production of Energy

Fatty acids provide a major energy source for the myocardium, skeletal muscle, and liver via β -oxidation, which occurs in the mitochondria.¹ Short-chain and medium-chain fatty acids can enter the mitochondria directly, but long-chain fatty acids (LCFAs) must be transferred in via a shuttle involving 3 enzymes/transporters and carnitine.² Once inside the mitochondrial matrix, β -oxidation progresses in a cycle of 4 steps, which result in the sequential cleavage of 2-carbon acetyl-coenzyme A (CoA) from the fatty acid chain and the transfer of electrons to the respiratory chain for adenosine triphosphate (ATP) production (Figure).^{2,3} Acetyl-CoA can be utilized as a substrate in the tricarboxylic acid (TCA) cycle to create additional reducing equivalents for the electron transport chain, or it can be utilized for ketone synthesis, an alternate form of energy for the brain, myocardium, muscle, kidney, and other tissues.² This energy is especially critical during periods of fasting when glucose is unavailable and during periods of physiologic stress. The metabolism of LCFAs to support creation of energy focuses on oxidation of acetyl-CoA in the mitochondrial TCA cycle.⁴ For proper TCA cycle function, inflow of substrates (anaplerosis) must be balanced by outflow (cataplerosis).⁵ In anaplerosis, intermediates are continuously replenished to sustain TCA cycle function and drive ATP production. With cataplerosis, other intermediates are removed to drive gluconeogenesis and lipogenesis.^{4,5} This balance is critical to maintaining energy homeostasis.^{4,6}

Fatty acids can be classified as even-chain or odd-chain based on the number of carbons in the α -carbon backbone. Fatty acids having an odd number of carbon atoms are minor physiologic species, with 16 and 18 carbon species predominating in food sources and tissue storage. Odd-chain fatty acids are oxidized identically to even-chain fatty acids, except that in the final round of β -oxidation, 1 molecule of each of acetyl-CoA and anaplerotic propionyl-Co are produced.⁷ The production of propionyl-CoA is specific to odd-carbon fatty acids and leads to their anaplerotic properties.⁸ Medium odd-chain fatty acids can restore energy production and improve cardiac and skeletal muscle function until odd-chain substrates become limiting, a problem eliminated by use of anaplerotic odd-chain fats.^{7,9}

ABSTRACT

Long-chain fatty acid oxidation disorders (LC-FAODs) are rare, life-threatening, autosomal recessive genetic disorders characterized by acute crises of energy production and chronic energy deficiency. Patients may present with rhabdomyolysis induced by exercise; fasting or illness; hepatic dysfunction, including severe hypoglycemia and hyperammonemia; and cardiomyopathy. These clinical manifestations can lead to frequent hospitalizations and premature death. LC-FAODs are caused by mutations in nuclear genes encoding mitochondrial enzymes involved in the conversion of dietary long-chain fatty acids (LCFAs) into energy during times of fasting and physiologic stress. Despite newborn screening, current management options leave many patients continuing to experience major clinical events, and mortality rates remain elevated. The current standard therapy for LC-FAODs is avoidance of fasting and supplementation of medium-chain triglyceride oil, an even, medium-chain fatty acid that does not require the typical steps of LC-FAOD for metabolism. Despite this therapy, patients with LC-FAODs continue to experience recurring hospitalizations, and high morbidity and mortality rates. In recent years, the use of medium, odd-chain fatty acids, such as triheptanoin, have been studied as a treatment of LC-FAODs due to its anaplerotic properties. Due to favorable safety and efficacy data from clinical trials, this novel agent has the potential to transform the treatment of LC-FAODs and improve patient outcomes in this patient population. This article provides an overview of the epidemiology, pathophysiology, clinical manifestations, and current management approaches for the diagnosis and management of LC-FAODs. It also provides the most recent clinical safety and efficacy data for triheptanoin and other therapies under investigation.

Am J Manag Care. 2020;26:S139-S146

For author information and disclosures, see end of text.

Overview of Long-Chain Fatty Acid Oxidation Disorders

Fatty acid oxidation disorders (FAODs) are a group of more than 20 life-threatening, inborn errors of metabolism caused by either disruption of entry of fatty acid substrates into mitochondria or a defect in their β -oxidation in the mitochondrial matrix.^{10,11} They are inherited as autosomal recessive conditions. Historically, they have been shown to lead to significant morbidity and mortality.⁹ Fatty acid oxidation (FAO) is characterized as long and medium, based on the α -carbon chain length of fatty acyl-CoA substrates. Long-chain fatty acid oxidation disorders (LC-FAODs) affect the metabolism of fats of greater than 8-12 carbons and are caused by deficiencies of 1 of 3 enzymes/carriers responsible for entry of long-chain fats into mitochondria (the carnitine cycle) or 4 steps of the mitochondrial β -oxidation spiral in the mitochondrial matrix. The end result is a deficit of reducing equivalents for mitochondrial oxidative phosphorylation. Symptoms in patients with LC-FAODs are driven by acute crises of energy production and chronic energy deficiency.^{8,12,13} In LC-FAODs, the oxidation of fatty acids is disrupted by deficiencies in crucial mitochondrial

enzymes, which in turn compromises energy homeostasis and sparks a buildup of potentially toxic fatty acid intermediates.⁴ Partial or incomplete oxidation of fatty acids leads to accumulation of elevated concentrations of metabolite intermediates in blood and organs as well as systemic effects, such as hypoglycemia, hyperammonemia, and acidosis.¹⁴ Common symptoms include cardiomyopathy and recurrent rhabdomyolysis.

Incidence and Mortality Rates Associated With LC-FAODs

LC-FAODs occur with an overall incidence of 1 in 9300 individuals in the United States, Australia, and Germany, with a similar incidence in the rest of the world.¹⁵ In the United States and many developed countries, FAODs are identified by newborn screening (NBS). Annually, there are an estimated 100 births with a confirmed diagnosis in the United States, with an estimated 2000 to 3500 individuals currently living with an LC-FAOD.¹⁶ Before NBS, mortality was as high as 60% to 90%.¹⁴ In patients identified by NBS, mortality is lower, but morbidity remains high, with recurrent symptoms and a negative impact on quality of life.^{8,10}

FIGURE. Metabolism of LCFAs³

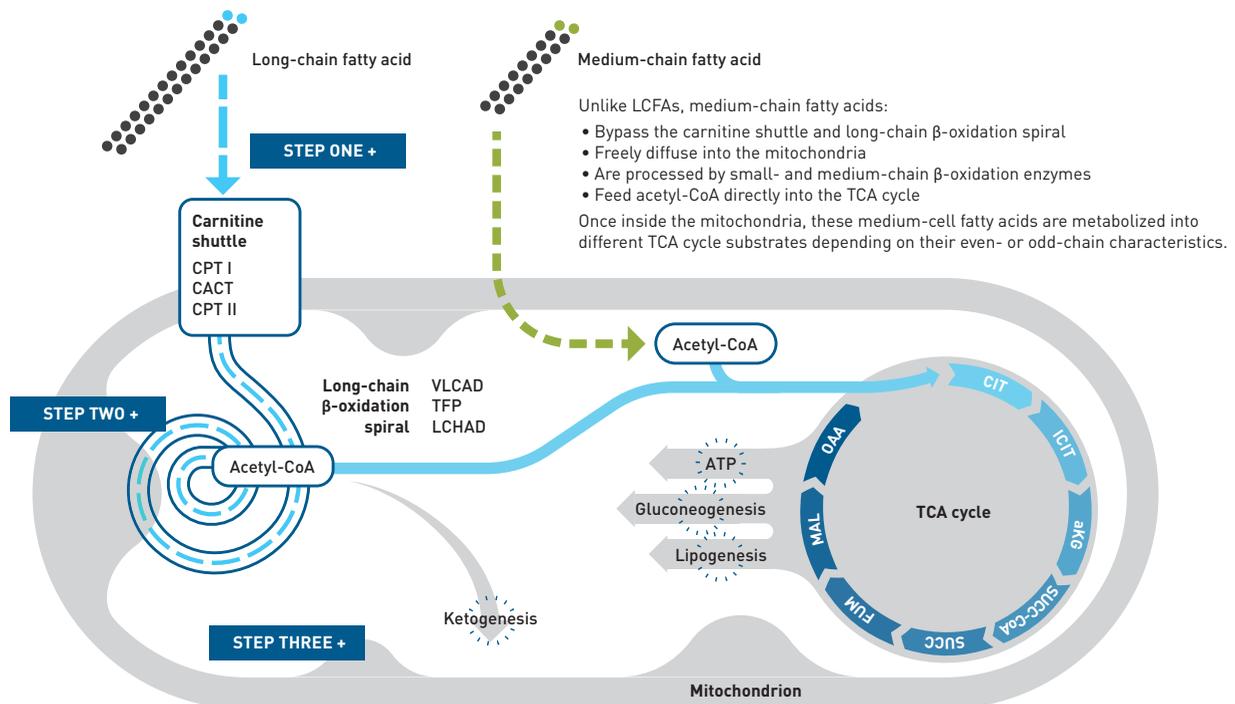


Image obtained from FAOD in Focus website. <https://www.faodinfofocus.com/hcp/mechanism-of-disease/>
Acetyl-CoA, acetyl coenzyme A; ATP, adenosine triphosphate; CACT, carnitine-acylcarnitine translocase deficiency; CPT 1, carnitine palmitoyltransferase I; CPT 2, carnitine palmitoyltransferase II; LCFA, long-chain fatty acid; LCHAD, long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency; TCA, tricarboxylic acid; TFP, trifunctional protein deficiency; VLCAD, very-long-chain acyl-CoA dehydrogenase deficiency.

Clinical Symptoms of LC-FAODs

The defects of LC-FAODs include both the carnitine cycle and the intramitochondrial β -oxidation cycle. They include carnitine palmitoyltransferase (CPT I or CPT II) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxy-acyl-CoA

dehydrogenase (LCHAD) deficiency, and trifunctional protein (TFP) deficiency (Table 1^{2,13,17-22}). Of these, VLCAD deficiency is the most common.⁴ In general, clinical symptoms are more similar than different among the disorders and, as discussed above, include hypoglycemia, hyperammonemia, recurrent rhabdomyolysis, and

TABLE 1. Summary of Select Long-Chain Fatty Acid Oxidation Disorders^{2,13,17-22}

Type	Causes	Incidence	Clinical presentation
Carnitine palmitoyltransferase I (CPT I) deficiency	Caused by mutations in the <i>CPT1A</i> gene encoding CPT IA, a liver isoform, preventing long-chain acyl-CoAs from entering mitochondria for fatty acid β -oxidation.	Fewer than 50 affected individuals have been identified; may be more common in the Hutterite and Inuit populations.	Birth to 18 months: related to liver metabolism and include hepatic encephalopathy, hypoketotic hypoglycemia, seizures, and sudden unexpected death in infancy; muscle and heart symptoms are absent.
Carnitine palmitoyltransferase II (CPT II) deficiency	Caused by mutations in the <i>CPT2</i> gene encoding CPT II. Prevents long-chain acyl-CoAs from being transported into mitochondria for fatty acid β -oxidation.	The lethal neonatal form has been described in at least 18 families, whereas the severe infantile hepatocardiomyopathy form has been identified in about 30 families. There have been more than 300 cases of the myopathic form. The late-onset form is the most frequent, with a common mutation in the Ashkenazi Jewish population.	Symptoms range from lethal neonatal to onset of muscular symptoms in adolescence or adulthood. A severe infantile hepatocardiomyopathy form is usually caused by one severe mutation and one mild. Major symptoms include hypoketotic hypoglycemia and cardiomyopathy in infantile and recurrent rhabdomyolysis in adolescents or young adults. Cardiomyopathy does not occur in late-onset disease.
Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	Mutations in the <i>ACADVL</i> gene cause VLCAD deficiency. VLCAD catalyzes the first intramitochondrial step of fatty acid β -oxidation.	VLCAD was originally described in 1992 and is now recognized as having an incidence of 1 in 40,000 to 120,000 individuals, depending on the population.	Clinically heterogeneous, with phenotypes varying from severe symptoms early in childhood, including hypoglycemia and hyperammonemia with high mortality; to adolescent- or adult-onset of skeletal muscle involvement including recurrent rhabdomyolysis and myoglobinuria. Symptoms transition from early to muscular in mid-childhood (ages 4-6 years). Cardiomyopathy can occur at any age. Symptoms are typically triggered by physiologic stress or fasting. In patients with VLCAD, specifically, the rate of sudden death has been reported at 52%, with an overall mortality of 60%.
Long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency	Caused by a common mutation in the <i>HADHA</i> gene encoding the α subunit of TFP. It catalyzes the third step of fatty acid β -oxidation in the mitochondrial matrix.	Incidence is unknown. One estimate, based on a Finnish population, indicates that 1 in 62,000 pregnancies is affected by this disorder. In the United States, the incidence is likely much lower.	Symptoms include infantile hypoketotic hypoglycemia with or without cardiomyopathy. As in VLCAD deficiency, recurrent rhabdomyolysis is a later symptom. Early death was common prior to newborn screening. In surviving patients, 65% experience skeletal myopathy with or without recurrent rhabdomyolysis, 21% develop peripheral neuropathy, and 43% have retinopathy.
Trifunctional protein (TFP) deficiency	Genetically heterogeneous, with mutations identified in both the <i>HADHA</i> and <i>HADHB</i> genes, leading to defects in all 3 of the enzymes that comprise the TFP complex.	Probably much less than 1 in 100,000 births; its true incidence is undetermined.	Early symptoms similar to LCHAD deficiency but often more severe. Peripheral neuropathy is generalized, severe, and can be devastating. Pigmentary retinopathy is less dramatic than in LCHAD deficiency.

acute or chronic cardiomyopathy (Table 2⁴). Cardiomyopathy can be dilated or hypertrophic. The cardinal finding of hypoketotic hypoglycemia is variable and may not manifest in the milder forms of each disease. Hypoglycemia tends to dominate the clinical picture in infants and younger children, with rhabdomyolysis becoming more common in older children (>6 years of age). Cardiomyopathy can occur at any age. Peripheral neuropathy and retinal degeneration are unique to LCHAD/TFP deficiencies.¹⁰

NBS of LC-FAODs

Historically, LC-FAODs could only be diagnosed symptomatically, often after sudden or near death, as all clinical parameters returned to normal when patients were well. A retrospective analysis of 187 clinically diagnosed patients with LC-FAODs concluded that mortality rates had not changed overall during the 3 decades before the publication.¹⁴ Even with an increased understanding of pathophysiology and evolving standard of care, overall there was greater than 50% mortality in each decade in patients who received a diagnosis symptomatically. The development of acylcarnitine analysis via mass spectrometry allowed identification of many patients who were asymptomatic, but some level of clinical suspicion was necessary before the test was ordered. More recently, the United States and many developed nations have incorporated FAODs into expanded NBS using tandem mass spectrometry,^{13,23} allowing identification of affected infants before the development of symptoms.⁴ NBS and early intervention have diminished mortality rates for patients with FAODs; however, most continue to experience substantial morbidity due to episodes of metabolic decompensation despite treatment.^{4,9,10}

Clinical Management of LC-FAODs

Even though the understanding of the pathophysiology of LC-FAODs has expanded considerably in the past few decades, treatments

for LC-FAODs have largely involved nutritional and symptomatic management. Historically, treatment has been consensus based as evidence-driven outcomes are limited.¹³ In June 2020, an agent specifically indicated for the treatment of pediatric and adult patients with LC-FAOD, triheptanoin (Dojolvi), was approved and will be discussed below along with agents under investigation.²⁴

The primary goal of nutrition management of LC-FAODs is to limit long-chain fat as a substrate for energy production, both by preventing β -oxidation and catabolism and by restricting the amount of dietary long-chain fat while still providing adequate nutrients for normal growth and development.¹⁰ The level to which fat is limited is reliant on the individual patient's gene mutation and disease severity. Patients with LC-FAODs in mild or moderate forms typically experience intermittent symptoms at times of augmented β -oxidation, such as while exercising or fasting.¹⁰ Routine fasting overnight is safe for most patients, with a maximum of 8 to 10 hours recommended by most guidelines.^{10,25} Medium-chain triglyceride (MCT) oil given 30 to 45 minutes before strenuous exercise decreases accumulation of long-chain fats. Additional intake of carbohydrates and fluids should occur every 2 hours. Early implementation of sick-day protocol is recommended when symptoms of an intercurrent illness are present or with the development of rhabdomyolysis.²⁵ Sick-day protocol can often be implemented at home with increased fluid and caloric intake to prevent catabolism, especially during febrile illnesses. However, if intake is inadequate or if myoglobinuria develops as detected with standard urinalysis dipsticks, then admission to the hospital is necessary. In the hospital, maintenance of caloric intake via an intravenous dextrose solution containing 10% dextrose with appropriate electrolytes at 1.5 times maintenance fluid infusion rate will provide 8 mg/kg/min of glucose, usually sufficient to suppress catabolism. Serum electrolytes, creatinine, and creatinine phosphokinase (CPK) should be monitored and treatment continued until the CPK is trending down. Decision to transition to enteral feeds and discharge from the hospital must be personalized.^{10,26}

The use of carnitine supplementation in LC-FAODs has not been well studied and is controversial.¹³ Supplementation is often considered if secondary carnitine deficiency develops; however, some rodent studies have suggested that long-chain hydroxyacylcarnitines may induce arrhythmias.¹⁰ Patients require at least 10% of dietary calories from long-chain fats to maintain normal essential fatty acid levels and may need essential fatty acid supplementation if levels are low. Docosahexaenoic acid (DHA) is crucial for brain, visual, and immune functions and prevention of fat-soluble vitamin deficiencies and should be supplemented in LCHAD/TFP deficiency.¹⁰

Management in Infancy

Some age-specific management issues should be considered in LC-FAODs. Nutritional management in infancy should deliver 40%

TABLE 2. Common Clinical Manifestations Associated With LC-FAODs⁴

- **Hypoketotic hypoglycemia**, often with hepatomegaly, increased transaminases, and hyperammonemia, possibly resulting in convulsions, coma, and brain damage, typically in infants and young pediatric patients.
- **Cardiomyopathy**, with initial hypertrophy of the left ventricle, and sometimes accompanied by pericardial effusion. Arrhythmias have been observed in all LC-FAODs, except those caused by CPT-IA deficiency, and may occur without cardiomyopathy.
- **Myopathy**, presenting with myalgia, muscle weakness, exercise intolerance, myoglobinuria, and recurrent rhabdomyolysis. Myopathy can manifest in young children, but is more typical in puberty or adulthood, triggered by heavy exercise, post-anesthesia, or a viral infection.

CPT-IA, carnitine palmitoyltransferase IA; LC-FAOD, long-chain fatty acid oxidation disorder.

to 45% of total energy from fat, with a minimum of 10% from long-chain fat (often increased to 20% in mild disease).^{10,27} Breast milk is high in fat content and breastfeeding may need to be halted in symptomatic infants.¹⁰ Infants with mild or asymptomatic disease may be able to breastfeed, but alternating breastfeeding with metabolic formula containing MCTs or supplementing pumped breast milk with metabolic formula may be considered. These formulas are often prescribed by a metabolic physician/specialist.¹⁰

Childhood and Adult Management

In childhood and adulthood, reduction of calories from fat to 30% to 35% of total energy is appropriate. In severe disease, the patient may still need to limit long-chain fat to 10% of total energy and provide MCTs for the remainder of the energy requirement.^{10,27} However, a 10% long-chain fat diet is difficult to follow and relaxation to 20% is often allowed, similar to that of patients with milder disease. As formulas for infants with FAODs are enriched with essential fatty acids, essential fats may need to be supplemented when infant formula is halted.¹⁰ Linoleic acid (C18:2n6) and α -linolenic acid (C18:3n3) should comprise 3% and 1% of energy and energy intake, respectively, typically through supplementation with specific oils, such as walnut or flaxseed oil.^{10,27} Patients are at risk for becoming deficient in fat-soluble vitamins and may need supplementation. Additionally, fasting limitations of 8 to 10 hours are often employed.^{10,28}

Proper Use of MCT Oils

Commercially available MCT oils consist of a mix of octanoate (C8:0), decanoate (C10:0), and some dodecanoate (C12:0) fatty acids esterified to a glycerol backbone with the proportions of these fatty acids varying from lot to lot.²⁸ Prescription forms of MCT are essentially pure trioctanoylglycerol. In general, the daily dose of MCTs should be equally divided across all meals, sometimes with a dose reserved before excessive physical activity. Infants on metabolic formula typically tolerate MCT oil without symptoms, but older patients starting treatment for the first time experience gastrointestinal symptoms, including abdominal discomfort, cramping, flatulence, bloating, and diarrhea. In this instance, reducing the daily dose and increasing slowly to the desired final dose usually resolves symptoms. MCTs can be mixed into a variety of foods and beverages. Additional recommendations for using MCT oils are found in [Table 3](#).²⁹

Recently Approved Therapy

Triheptanoin

Following the discovery of LC-FAODs, it was generally assumed that supplementation for these patients with MCT oil would prevent clinical symptoms, as the even-chain fats it contained could completely bypass the metabolism. However, clinical symptoms persisted in patients, and is now recognized to be due at least in

part to depletion of odd-chain TCA cycle intermediates and subsequent persistent energy deficiency. In recognition of this deficit, triheptanoin, a food-grade supplemental heptanoyl-triglyceride, was proposed as a more physiologically balanced MCT as 2 cycles of FAO produced both 2- and 3-carbon intermediates. Early case reports on efficacy led to a significant compassionate-use experience with the medication. Two retrospective studies demonstrated considerable improvement in treated patients, specifically reductions in episodes and hospital days related to hypoglycemia, cardiomyopathy, and rhabdomyolysis.^{12,30} This, in turn, led to the development and FDA approval of pharmaceutical-grade triheptanoin. Triheptanoin is available commercially as an oral liquid supplied in a 500-mL bottle (supplying 8.3 kcal/mL). The target daily dose is up to 35% of the patient's total prescribed daily caloric intake divided into 4 or more doses administered at mealtimes or with snacks. Initial doses are 10% of the daily caloric intake and slowly increased to the target of 35% over 2 to 3 weeks.²⁴ Upon ingestion, triheptanoin is rapidly digested to heptanoate in the small intestine and absorbed into the circulation. As with other medium-chain fats, heptanoate can diffuse across the mitochondrial membrane and be metabolized by the medium-chain-specific enzymes of FAO, bypassing the need for the carnitine cycle, the long-chain transport, and long-chain-specific enzymes.⁸ The 3-carbon propionyl-CoA product of FAO is further metabolized to succinyl-CoA and succinate, resupplying the TCA cycle intermediates that are secondarily deficient in patients and restoring the ATP production necessary for gluconeogenesis.^{8,31}

Clinical Trials of Triheptanoin/UX007

Clinical trials have assessed the safety and efficacy of triheptanoin in the treatment of LC-FAODs. The first was a double-blinded, randomized controlled study that compared changes in physiologic function after treatment with pharmaceutically pure octanoyl or

TABLE 3. Recommended Guidelines for Using MCT Oil²⁹

- Do not surpass 4-7 tablespoons per day (60-100 mL/day) for gastrointestinal tolerance.
- Divide the daily dosage equally between all meals. If eating 3 meals a day, this can be 1 or 2 tablespoons per meal.
- Do not heat MCT oil over 150°C (302°F); otherwise, it will affect the flavor of the food.
- Mix MCT oil into a variety of foods and beverages (eg, hot cereals, soups, sauces, broth, smoothies, fruit/vegetable juices, hot chocolate, coffee, tea).
- If administered through a feeding tube, 1 tablespoon of MCT oil can be given with a water flush of 30 mL before and after its administration.
- MCT supplementation should never be the only source of fat >3 weeks. After 3 weeks, high EFA-containing vegetable oil should be included in the diet to reduce risk of EFA deficiency.

EFA, essential fatty acid; MCT, medium-chain triglyceride.

heptanoylglycerol in a double-blind fashion in 32 participants. Patients in the C7 (triheptanoin) group experienced increased left ventricular (LV) ejection fraction by 7.4% ($P = .046$) while experiencing a 20% ($P = .041$) decrease in LV wall mass on their resting echocardiogram. They also required a lower heart rate (average = 6.98 beats per minute [bpm]) for the same amount of work during a moderate-intensity exercise stress test when compared with patients taking C8 (trioctanoin) (95% CI, 0.34-13.63 bpm; $P = .040$). There was no significant difference in total energy expenditure, phosphocreatine recovery with acute exercise, body composition, incidence of rhabdomyolysis, or any secondary outcome measures between the groups. There were no significant differences in

adverse effects (AEs) between C7 and C8, and the majority were minor and gastrointestinal in nature. The improvement in cardiac function in hearts with no obvious dysfunction is in keeping with improved cardiac outcomes in other clinical trials, whereas the lack of a difference in clinical outcomes reflects the short duration of the study and the relative stability of patients entering the study.²⁸ The second trial was a retrospective analysis of data from 20 of a total of 24 patients with LC-FAOD who were enrolled in a compassionate use protocol and treated with triheptanoin for up to 13 years. Hospitalization event rates, number of hospitalization days per year, and event rates for rhabdomyolysis, hypoglycemia, and cardiomyopathy were collected and compared before and after triheptanoin initiation (Table 4¹²). A total of 320 hospitalizations were documented for 20 subjects from birth through the end of the study period. Mean hospitalization days per year decreased significantly by 67% after triheptanoin initiation (17.55 vs 5.76; $P = .0242$). Additionally, hypoglycemia events were nearly eliminated with a significant reduction in events per year and hospital days per year. Rhabdomyolysis events and hospitalization days trended down but were non-significantly changed with addition of triheptanoin. The data collected related to cardiomyopathy symptoms were insufficient to assess for impact of triheptanoin administration. AEs related to treatment with triheptanoin in the 20 patients included diarrhea (60%), gastrointestinal upset (55%), frequent loose stools (15%), and lethargy (10%).¹²

Results of a study for FDA registration of triheptanoin have also been published. This study was a single-arm, open-label, multicenter phase 2 safety and efficacy study evaluating patients with severe LC-FAOD evidenced by ongoing related musculoskeletal, cardiac, and/or hepatic events despite treatment; end points were at 24 and 78 weeks. Patients acted as their own control. After a 4-week run-in on current therapy, triheptanoin was titrated to a target dose

TABLE 4. Impact of Triheptanoin/UX007 on Major Medical Events¹²

Major medical events	n	Pre UX007 vs with UX007; % change (<i>P</i> value)
Mean total hospitalizations/year ^a	16	1.94 vs 1.26; -35% ($P = .1126$)
Mean total hospital days/year ^{a,b}	15	17.55 vs 5.76; -67% ($P = .0242$)
Mean hypoglycemia events/year ^{a,b,c}	9	0.92 vs 0.04; -96% ($P = .0091$)
Mean hypoglycemia total hospital days/year ^{a,c}	9	8.42 vs 0.18; -98% ($P = .0257$)
Mean rhabdomyolysis events/year ^{a,d}	11	1.05 vs 0.68; -35% ($P = .4604$)
Mean rhabdomyolysis total hospital days/year ^{a,d}	9	5.94 vs 2.36; -60% ($P = .1224$)

^a Excludes data for 4 infants dosed within first 6 months of life.

^b Excludes hospitalizations with unknown discharge dates.

^c Includes only those patients with hypoglycemia events prior to treatment.

^d Includes only those patients with rhabdomyolysis events prior to treatment.

TABLE 5. Impact of Triheptanoin/UX007 on Major Clinical Events^{8,13}

Major clinical events (MCEs) at 78 weeks (n = 29)	Annualized event rate (number of events/year)	Annualized duration rate (number of days/year)	Total events
	Pre UX007 vs with UX007; % change (<i>P</i> value)	Pre UX007 vs with UX007; % change (<i>P</i> value)	Pre UX007 vs with UX007; % change
All MCEs (mean)	1.69 vs 0.88; -48.1% ($P = .021$)	5.96 vs 2.96; -50.3% ($P = .028$)	70 vs 39 -44.3%
All hospitalization events (mean)	1.39 vs 0.65; -53.1% ($P = .016$)	5.66 vs 2.74; -51.6% ($P = .032$)	57 vs 29 -49.1%
Rhabdomyolysis (mean of all events)	1.30 vs 0.83; -36.1% ($P = .119$)	3.95 vs 2.79; -29.3% ($P = .204$)	55 vs 37 -32.7%
Hypoglycemia (mean of all events)	0.32 vs 0.02; -92.8% ($P = .068$)	1.41 vs 0.02; -98.4% ($P = .085$)	12 vs 1 -91.7%
Cardiomyopathy (mean of all events)	0.07 vs 0.02; -69.6% ($P = .309$)	0.60 vs 0.15; -75.1% ($P = .288$)	3 vs 1 -66.7%

of 25% to 35% of total daily caloric intake. The incidence of and hospitalizations related to hypoglycemia, cardiomyopathy, and rhabdomyolysis were captured and compared with the year prior to starting in the study. Patients also were evaluated on several age/condition-eligible end points, including submaximal exercise tests to assess muscle function/endurance 12-minute walk test (12MWT), exercise tolerance (cycle ergometry), and health-related quality of life (HRQOL). Twenty-nine patients (0.8-58 years) were enrolled; most qualified based on severe musculoskeletal disease. Twenty-five patients (86%) completed the 24-week treatment period. At week 18, eligible patients ($n = 8$) demonstrated a 28% increase (LS mean = +181.9 meters; $P = .087$) from baseline (673.4 meters) in 12MWT distance. At week 24, eligible patients ($n = 7$) showed a 60% increase in watts (W) generated (LS mean = +409.3W; $P = .149$) over baseline (744.6W) for the exercise tolerance test. Improvements in exercise tests were supported by significant improvements from baseline in the adult ($n = 5$) self-reported SF-12v2 physical component summary score (LS mean = +8.9; $P < .001$). In patients with severe LC-FAOD, triheptanoin interim study results revealed enhanced exercise endurance and tolerance and was linked with positive changes in self-reported HRQOL.⁹ At 78 weeks, there was a demonstrated persistent reduction of the incidence of major clinical events and related hospital days related to rhabdomyolysis, hypoglycemia, and cardiomyopathy. The composite end points of annualized event rate and annualized duration rate for all events were significantly reduced as noted in **Table 5**.^{8,13} The majority of AEs over both studies were mild to moderate gastrointestinal symptoms, including diarrhea (44%), vomiting (44%), nausea (14%), and abdominal pain (including abdominal discomfort, abdominal distention, upper abdominal pain, and gastrointestinal pain (60%). AEs led to dose reductions in 35% of patients in the first study and 12% of patients in the extension study. AEs were often managed with smaller, frequent doses mixed with food.^{8,24}

Subsequently, 75 patients from previous studies were enrolled in a long-term safety extension and efficacy open-label phase 2 study. Patients will begin or continue treatment with triheptanoin while maintaining other dietary restrictions. Primary outcome measures of this study include annualized LC-FAOD major clinical events (rhabdomyolysis, hypoglycemia, and cardiomyopathy) through 84 months on treatment and monitoring for number of treatment-emergent AEs or serious AEs. This study is underway with an estimated completion date of September 2021.³²

Agents Under Development

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily, ligand-modulated transcription factors that regulate gene expression of many cellular processes. The 3 PPARs, α , γ , and δ , are activated by lipids and are targets for current drug therapies.³³ PPAR α is primarily expressed in the

liver, where it upregulates genes involved in lipid oxidation in the fasted state.³⁴⁻³⁶ PPAR γ is highly expressed in adipose tissue and regulates adipogenesis and insulin sensitivity.³⁷ PPAR δ controls genes involved in cellular metabolic processes, such as glucose homeostasis, fatty acid mobilization and oxidation, and electron transport chain. PPAR δ is expressed in metabolically active tissues, including liver, muscle, and fat.³⁸

Bezafibrate, a relatively broad-spectrum PPAR agonist that increases expressions of a number of FAO genes, has been investigated as a treatment for FAODs.²⁵ Three clinical trials of bezafibrate have produced contradictory findings. The first trial, which was an open-label, 6-month pilot study with a 3-year extension, showed increased level of whole-body fat oxidation, improved QOL scores, reduced creatinine kinase levels, and diminished occurrence of rhabdomyolysis with bezafibrate.^{39,40} Results of a double-blind, randomized, placebo-controlled study failed to demonstrate a benefit of bezafibrate over placebo in clinical symptoms or FAO capacity during exercise.⁴¹ Finally, frequency of myopathic attacks was not reduced in an open-label study; however, QOL scores were improved.^{25,42} To date, there are no active trials for bezafibrate.

In September 2019, the FDA granted orphan drug designation to REN001, a selective PPAR γ agonist, for the treatment of FAODs. REN001 is currently being investigated in a phase 1b trial involving 12 patients with confirmed FAODs. The primary outcome measure of the study is to assess the safety and tolerability of REN001.⁴³

Conclusions

LC-FAODs are a heterogeneous group of disorders that have seen some improvement in clinical outcomes through early identification of patients with NBS but remain problematic, nonetheless. Traditional therapies still leave patients at risk for episodes of hypoglycemia, cardiomyopathy, and rhabdomyolysis common to all LC-FAODs, along with peripheral neuropathy and pigmentary retinopathy in LCHAD/TFP deficiencies. The recent FDA approval of triheptanoin is likely to improve—but not eliminate—these clinical problems. Available clinical studies demonstrate that triheptanoin directly addresses TCA cycle deficiencies that arise in LC-FAODs and improves clinical outcomes with reduction in clinical symptoms and hospital days. As such, triheptanoin represents a substantial breakthrough that will greatly improve the treatment and management of LC-FAODs. Thus, patients will continue to need careful monitoring by a team of experienced metabolic care providers working in close collaboration with patients' primary care providers. Patients' access to educational, financial, and support resources are also clear needs, given the long-term implications and the need for chronic access to the healthcare system. □

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Funding source: This activity is supported by an educational grant from Ultragenyx Pharmaceutical Inc.

Author disclosure: Dr Vockley has the following relevant financial relationships with commercial interests to disclose:

Grant/Research support – Reneo Pharmaceuticals, Ultragenyx Pharmaceutical Inc

Authorship information: Substantial contributions to the concept and design; analysis and interpretation of data; and critical revision of the manuscript for important intellectual content.

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REFERENCES

1. Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *Biochim Biophys Acta*. 2016;1863(10):2422-2435. doi: 10.1016/j.bbamcr.2016.01.023
2. Sun A, Merritt JL II. Orphan drugs in development for long-chain fatty acid oxidation disorders: challenges and progress. *Orphan Drugs: Res Rev*. 2015;5:33-41. doi: 10.2147/ODRR.S63061
3. Healthy fatty acid oxidation. FAOD in Focus. Accessed July 10, 2020. faodinfocus.com/hcp/mechanism-of-disease
4. Knottnerus SJ, Bleeker JC, Wüst RC, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. *Rev Endocr Metab Disord*. 2018;19(1):93-106. doi: 10.1007/s11154-018-9448-1
5. Owen OE, Kalhan SC, Hanson RW. The key role of anaplerosis and cataplerosis for citric acid cycle function. *J Biol Chem*. 2002;277(34):30409-30412. doi: 10.1074/jbc.R200006200
6. Brunengraber H, Roe CR. Anaplerotic molecules: current and future. *J Inherit Metab Dis*. 2006;29(2-3):327-331. doi: 10.1007/s10545-006-0320-1
7. Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. *J Clin Invest*. 2002;110(2):259-269. doi: 10.1172/JCI15311
8. Vockley J, Burton B, Berry GT, et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). *J Inherit Metab Dis*. 2019;42(1):169-177. doi: 10.1002/jimd.12038
9. Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab*. 2017;120(4):370-377. doi: 10.1016/j.ymgme.2017.02.005
10. Merritt JL II, Norris M, Kanungo S. Fatty acid oxidation disorders. *Ann Transl Med*. 2018;6(24):473. doi: 10.21037/atm.2018.10.57
11. Shekhawat PS, Matern D, Strauss AW. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. *Pediatr Res*. 2005;57(5 Pt 2):78R-86R. doi: 10.1203/01.PDR.0000159631.63843.3E
12. Vockley J, Marsden D, McCracken E, et al. Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment—a retrospective chart review [published correction appears in *Mol Genet Metab*. 2015;116(3):221]. *Mol Genet Metab*. 2015;116(1-2):53-60. doi: 10.1016/j.ymgme.2015.06.006
13. Spiekeroetter U, Lindner M, Santer R, et al. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. *J Inherit Metab Dis*. 2009;32(4):488-497. doi: 10.1007/s10545-009-1125-9
14. Baruteau J, Sachs P, Broue P, et al. Clinical and biological features at diagnosis in mitochondrial fatty acid beta-oxidation defects: a French pediatric study of 187 patients. *J Inherit Metab Dis*. 2013;36(5):795-803. doi: 10.1007/s10545-012-9542-6
15. Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. *J Inherit Metab Dis*. 2010;33(5):521-526. doi: 10.1007/s10545-010-9076-8
16. Diagnosing LC-FAOD. FAOD in Focus. 2020. Accessed July 10, 2020. faodinfocus.com/diagnosis
17. Taggart RT, Smail D, Apolito C, Vladutiu GD. Novel mutations associated with carnitine palmitoyltransferase II deficiency. *Hum Mutat*. 1999;13(3):210-220. doi: 10.1002/(SICI)1098-1004(1999)13:3<210::AID-HUMU5>3.0.CO;2-D
18. Carnitine palmitoyltransferase I deficiency. Genetics Home Reference. Reviewed April 2014. Published June 9, 2020. Accessed June 22, 2020. ghr.nlm.nih.gov/condition/carnitine-palmitoyltransferase-i-deficiency#
19. Carnitine palmitoyltransferase II deficiency. Genetics Home Reference. Reviewed June 2014. Published June 9, 2020. Accessed June 22, 2020. ghr.nlm.nih.gov/condition/carnitine-palmitoyltransferase-ii-deficiency#genes
20. Very long-chain acyl-CoA dehydrogenase deficiency. Genetics Home Reference. Reviewed February 2018. Published June 9, 2020. Accessed June 22, 2020. ghr.nlm.nih.gov/condition/very-long-chain-acyl-coa-dehydrogenase-deficiency#definition
21. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Genetics Home Reference. Reviewed May 2017. Published June 9, 2020. Accessed June 2020. ghr.nlm.nih.gov/condition/long-chain-3-hydroxyacyl-coa-dehydrogenase-deficiency#statistics
22. Mitochondrial trifunctional protein deficiency. Genetics Home Reference. Reviewed September 2019. Published June 9, 2020. Accessed June 22, 2020. ghr.nlm.nih.gov/condition/mitochondrial-trifunctional-protein-deficiency#genes
23. Rocha H, Castineiras D, Delgado C, et al. Birth prevalence of fatty acid β -oxidation disorders in Iberia. *JIMD Rep*. 2014;16:89-94. doi: 10.1007/8904_2014_324
24. Dojlovi. Prescribing information. Ultragenyx Pharmaceutical Inc; 2020. Accessed July 15, 2020. ultragenyx.com/medicines/dojlovi-full-prescribing-information/
25. Yamada K, Taketani T. Management and diagnosis of mitochondrial fatty acid oxidation disorders: focus on very-long chain acyl-CoA dehydrogenase deficiency. *J Hum Genet*. 2019;64(2):73-85. doi: 10.1038/s10038-018-0527-7
26. Aldubayan SH, Rodan LH, Berry GT, Levy HL. Acute illness protocol for fatty acid oxidation and carnitine disorders. *Pediatr Emerg Care*. 2017;33(4):296-301. doi: 10.1097/PEC.0000000000001093
27. Rohr F, van Calcar S. Very long chain acyl CoA dehydrogenase deficiency (VLCADD). Genetic Metabolic Databases International: Nutrition Guidelines. Updated September 4, 2008. Accessed May 20, 2020. gmd.org/Resources/Nutrition-Guidelines/VLCAD
28. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. *J Inherit Metab Dis*. 2017;40(6):831-843. doi: 10.1007/s10545-017-0085-8
29. Shah ND, Limketkai BN. The use of medium-chain triglycerides in gastrointestinal disorders. *Practical Gastro*. Published February 2017. Accessed May 20, 2020. med.virginia.edu/ginutrition/wp-content/uploads/sites/199/2014/06/Parrish-February-17.pdf
30. Vockley J, Charrow J, Ganesh J, et al. Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. *Mol Genet Metab*. 2016;119(3):223-231. doi: 10.1016/j.ymgme.2016.08.008
31. Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM. Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain. *J Cereb Blood Flow Metab*. 2013;33(2):175-182. doi: 10.1038/jcbfm.2012.151
32. Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Extension Study for Subjects Previously Enrolled in Triheptanoin Studies. Updated June 4, 2020. Accessed July 10, 2020. clinicaltrials.gov/ct2/show/NCT02214160
33. Hansen MK, Connolly TM. Nuclear receptors as drug targets in obesity, dyslipidemia and atherosclerosis. *Curr Opin Investig Drugs*. 2008;9(3):247-255.
34. Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. *Proc Natl Acad Sci U S A*. 1997;94(9):4312-4317. doi: 10.1073/pnas.94.9.4312
35. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J Clin Invest*. 1993;103(11):1489-1498. doi: 10.1172/JCI6223
36. Xu HE, Lambert MH, Montana VG, et al. Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol Cell*. 1999;3(3):397-403. doi: 10.1016/s1097-2765(00)80467-0
37. Hevener AL, He W, Barak Y, et al. Muscle-specific Pparg deletion causes insulin resistance. *Nat Med*. 2003;9(12):1491-1497. doi: 10.1038/nm956
38. Oliver WR Jr, Shenk JL, Snaith MR, et al. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A*. 2001;98(9):5306-5311. doi: 10.1073/pnas.091021198
39. Bonnefont JP, Bastin J, Behin A, et al. Bezafibrate for an inborn mitochondrial beta-oxidation defect. *N Engl J Med*. 2009;360(8):838-840. doi: 10.1056/NEJMc0806334
40. Bonnefont JP, Bastin J, Laforet P, et al. Long-term follow-up of bezafibrate treatment in patients with the myopathic form of carnitine palmitoyltransferase 2 deficiency. *Clin Pharmacol Ther*. 2010;88(1):101-108. doi: 10.1038/clpt.2010.5
41. Ørngreen MC, Madsen KL, Preisler N, Andersen G, Vissing J, Laforet P. Bezafibrate in skeletal muscle fatty acid oxidation disorders: a randomized clinical trial. *Neurology*. 2014;82(7):607-613. doi: 10.1212/WNL.0000000000000118
42. Shirashi H, Yamada K, Oki E, et al. Open-label clinical trial of bezafibrate treatment in patients with fatty acid oxidation disorders in Japan; 2nd report QOL survey. *Mol Genet Metab Rep*. 2019;20:100496. doi: 10.1016/j.ymgmr.2019.100496
43. A Study of the Safety of RENO01 in Patients With Fatty Acid Oxidation Disorders. Updated August 26, 2019. Accessed July 15, 2020. clinicaltrials.gov/ct2/show/NCT03833128

Long-Chain Fatty Acid Oxidation Disorders: Managed Care and Specialty Pharmacy Implications

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The Burden of Long-Chain Fatty Acid Oxidation Disorders

The oxidation of fatty acids provides almost 80% of the energy required by body organs, including the heart, liver, and skeletal muscle, especially during periods of fasting when tissue glycogen stores decrease. During fasting or periods of moderate exercise or stress, the oxidation of fatty acids provides energy for cardiac and skeletal muscle while sparing glucose for use by the brain and central nervous system. Fatty acid oxidation disorders (FAODs) comprise more than 20 defects in mitochondrial β -oxidation and fatty acid transport and are inherited in an autosomal recessive pattern.^{1,2} Newborn testing for FAODs varies from state to state in the United States, but experience over time with this screening has demonstrated that the overall combined incidence of FAODs within the United States, Australia, and Germany encompasses a total of 5,256,999 newborns, delineated as a combined incidence of approximately 1:9300 live births.^{3,4}

Long-chain fatty acids (LCFAs) encompass most fatty acids in both the human diet and body stores, with more than 15 enzymes involved in their oxidation processes. Genetic mutations in genes encoding these enzymes lead to long-chain fatty acid oxidation disorders (LC-FAODs), resulting in derangements in energy homeostasis. LC-FAODs are now more easily screened for after birth and many asymptomatic individuals with these disorders are identified, but many patients still develop symptoms. These symptoms appear during catabolic situations, such as fasting, leading to a heterogeneous variety of presentations, including hypoketotic hypoglycemia, liver dysfunction, rhabdomyolysis, cardiomyopathy, and even early death.⁵ Dietary therapy is used most frequently to manage patients with LC-FAODs, but treatment varies depending on the individual disorder and severity of the underlying enzyme deficiency. The actual effectiveness of therapy is typically reported on a case-by-case basis instead of controlled clinical trials. However, one retrospective study of 187 patients diagnosed with LC-FAODs demonstrated that overall mortality rates have not changed significantly over the past 3 decades, even with improvements in patient management. Overall, mortality remains greater than 50% in each decade, and some indications have

ABSTRACT

Long-chain fatty acid oxidation disorders (LC-FAODs) represent a group of rare inborn errors of metabolism characterized by acute crises of energy metabolism and severe energy deficiency. Clinical manifestations include rhabdomyolysis, liver dysfunction, severe hypoglycemia, and cardiomyopathy. The symptoms associated with these genetic disorders may result in frequent hospitalizations and early death. Many patients with LC-FAODs experience major clinical events and significant morbidity and mortality that portends a substantial need for better therapeutic options for these disorders. Triheptanoin was recently approved for the treatment of LC-FAODs. As with any novel agent for rare diseases, the treatment adoption and coverage criteria for rare disease therapy such as this presents challenges for managed care decision makers. Both managed care decision makers and specialty pharmacists must ensure that healthcare professionals provide appropriate patient and caregiver education surrounding the management of LC-FAODs, including vital information on adopting emerging agents into the therapy armamentarium for these disorders.

Am J Manag Care. 2020;26:S139-S145

For author information and disclosures, see end of text.

shown higher mortality rates ranging from 60% to 95% during the review period. Newborn screening and early treatment may reduce mortality and improve outcomes but data from long-term studies are not available and patients with LC-FAODs continued to experience a major decompensation rate of about 25% despite diagnosis and standard treatment in the 2 years post birth in one study.⁶⁻⁸

Previous data have outlined the hospitalization burden associated with LC-FAODs. For example, data on long-term outcomes in patients with LC-FAODs demonstrated that patients averaged 1.94 hospitalizations annually for their disease, with 17.55 mean total hospital days per year. Hospitalization for rhabdomyolysis events was estimated at 1.05 events annually and hospitalization for hypoglycemia events was estimated at 0.92 events per year.⁶ More recent data from the triheptanoin Early Access Program (EAP) showed that among 91 patients with LC-FAODs who were critically ill before receiving triheptanoin therapy, 51% had rhabdomyolysis, 37% had cardiomyopathy, and 15% had hypoglycemia. Most patients also experienced multiple events and recurrent metabolic crises despite other treatment before administration of the protocol drug.⁹ Other data have linked LC-FAODs to a chronic cardiac disease phenotype and hypertrophic remodeling of the heart triggered by a mild yet chronic energy deficiency.¹⁰ These data emphasize a need for better and more individualized treatment strategies to prevent this type of decompensation that can result in hospitalization and significant morbidity and mortality.^{6,9}

Quality of Life Impact

There is limited information regarding the impact of the symptoms associated with LC-FAODs on quality of life (QOL) in affected patients and families compared with healthy peers.¹¹ However, various publications have revealed that patients with LC-FAODs experience substantially diminished health-related QOL (HRQOL) with negative impacts on physical, mental/emotional, and social functioning.^{12,13} In one study, Siddiq et al investigated the caregiver experiences of those with children with inherited metabolic diseases, its impact on child and family health, and interactions with the healthcare system.¹⁴ Investigators determined that many patients and caregivers experience increased stress and anxiety and have uncertainty and fear about the condition itself as well as long-term consequences.¹⁴ It is important to note that parents and caregivers of a chronically ill child are at greater risk of a lower HRQOL, experience more posttraumatic stress symptoms, and report higher levels of distress than parents of healthy children. Studies indicate that parental psychosocial problems affect the well-being of the child.¹¹ In addition, although there are some limited data from early attempts at patient follow-up, more systematic monitoring of HRQOL and the psychosocial impact of LC-FAODs is needed in the future, including the functioning of patients in daily practice and comparison of their QOL to that of the general population.¹¹

The Economic Burden of Rare Diseases and Their Management

Rare Disease Numbers and Statistics

Although the approximate incidence and prevalence of LC-FAODs has been enumerated, data surrounding the economic burden presented by these disorders are markedly lacking. An indirect comparison exploring rare disease in general can be made to assess the economic burden and costs of care associated with such disorders, including potential new therapies in development. Statistics compiled by America's Biopharmaceutical Companies notes that more than 30 million individuals in the United States are living with some form of rare disease. Rare disease is usually defined as affecting fewer than 200,000 people in the United States and may be acute or chronic in nature. The compiled statistics outline the challenging nature of these diseases.¹⁵

- Approximately 7000 rare diseases have been identified; however, just 5% of them have documented treatments available. Most of these diseases are life-threatening, emphasizing the need for new pharmacologic agents for therapy.
- More than 600 orphan drugs have been approved by the FDA since the passage of the Orphan Drug Act in 1983. This is in comparison to the fact that fewer than 10 agents had been approved for rare diseases in the decade prior to this legislation.
- A critical factor impacting new drug development is that 80% of rare diseases are genetic in origin. Progress in delineating these diseases at the molecular and genetic levels is crucial to drug development and advances in therapy, but it is important to note that the underlying causes of many rare diseases remain unclear.
- Approximately 560 agents are currently undergoing development for the treatment of rare diseases, encompassing a variety of disorders and organ systems.

The Economic Burden of Rare Diseases: Minimal Data and Potential Frameworks for Analysis

Data surrounding the economic burden of rare diseases are lacking, which is also the case for LC-FAODs. One European analysis, the Social Economic Burden and Health-Related Quality of Life in patients with Rare Diseases in Europe study, assessed direct and indirect costs of 10 rare diseases ranging from the more common cystic fibrosis to the rarer Prader-Willi syndrome. The results showed that the cost evidence on rare diseases is very scarce. The more common rare conditions (eg, cystic fibrosis, hemophilia) were better studied, but others had very limited cost information available. Total lifetime costs were found across 4 diseases and 5 disorders. Data availability correlated with the existence of a pharmacologic therapy for the disease, and indirect costs accounted for a substantial portion of the total healthcare costs. Additionally, most of the rare diseases

studied were associated with significant direct and indirect costs in terms of economic burden.¹⁶

Delineating the actual economic burden of rare disease goes beyond looking at direct and indirect costs incurred, as seen with many more common disorders. Rare diseases have fiscal impacts beyond healthcare costs. A study of the disorder hereditary transthyretin-mediated amyloidosis outlined a significant public health burden beyond the standardly measured healthcare costs. This study developed a fiscal cost model based on frameworks used to evaluate both disease burden and investments in healthcare technologies. Using a model evaluating patient income and subsequent tax payments, they assessed different scenarios based on disease onset, diagnosis, progression, and survival in terms of healthcare costs, government benefits paid to the patient, and the patient's tax payment contributions over their lifetime. Different scenarios provided different economic results. As an example, a patient who received an early diagnosis and then exhibited median disease progression but an early death paid fewer taxes but received more in terms of pensions, disability payments, and healthcare than the general population. Such fiscal models can inform stakeholders how changes in morbidity and mortality from different patient scenarios can impact costs and expenditures, including public costs beyond the usually analyzed healthcare costs.^{17,18}

Evaluating the Economics for Rare Disease Management: The Rise of Specialty Therapies

Over the past few years, the FDA has approved a substantial number of treatments for rare diseases. Most healthcare stakeholders want to see a continual progression of rare disease research and therapy development; however, treatment of these disorders, especially those with an underlying genetic basis, can have prohibitively high costs. These costs can make investment in research and development difficult at best, and the debate surrounding payment strategies and pricing models to address the high cost of rare disease therapy is ongoing.¹⁹

The overall global market for orphan drugs is in a period of marked acceleration. Worldwide sales of orphan drugs reached a peak of \$100 billion in 2015, and that value is expected to more than double by 2022. By that point, these drugs will represent more than one-fifth of all prescription drug sales.^{20,21} More recent data from the annual analysis done by EvaluatePharma predicts approximately \$217 billion in sales from orphan drugs in 2024.²² One key factor that drives orphan drug spending has been the higher acquisition costs associated with these agents. A recent study showed the annual costs for orphan agents to be as much as 5 times higher than for nonorphan drugs, estimated at \$140,443 versus \$27,756, respectively.^{20,21} In the United States, the use of orphan agents has been enhanced by legislative and regulatory incentives. Additionally,

orphan therapies have not always been associated with barriers to insurance coverage due to the small patient population impacted and the lack of alternative therapies.²⁰ However, while the patient populations may be small, it remains that billions of dollars are invested into performing clinical trials, regulatory approval, and marketing and commercialization of new agents for treatment of rare diseases. Payers and health systems in the United States have not actually made enough effort to understand if and how rare diseases require special considerations or how to adapt more standard methods of health technology assessment and economic evaluation to fit rare disease management. Multiple factors come into play when considering a new agent or technology, including²⁰:

- Nature of the rare disease, including impact on patients and caregivers
- Impact of the new technology (eg, benefits vs risks, robustness of research evidence)
- Budget impact for specialized services
- Impact of the new technology beyond health benefits (eg, personal social services)
- Impact of the new technology on delivery of specialized services (eg, staff training to use the new technology)

One such rare disease evaluation framework was developed in Canada for use in making decisions surrounding rare disease and associated therapy funding. The framework created by the Ontario Public Drug Program consists of 7 steps, with sustainability based on adequate evidence from clinical studies about the emerging agent, including the feasibility of clinical trials given the disease rarity and a threshold for rarity of the disorder itself (Figure²³). The natural history of the disease must be reviewed along with the purported effectiveness of the new agent to fully delineate elements of the agent's effect. Potential long-term effectiveness can then be integrated into the disease model to assess uncertainty and costs can be incorporated via a budget impact model.²³⁻²⁵

There is also updated information available from the Institute for Clinical and Economic Review (ICER) surrounding treatments for ultrarare diseases (defined as affecting fewer than 10,000 individuals in a population). Although they will neither change their approach to rating evidence using their own matrix nor require different standards of evidence, ICER will provide specific content surrounding potential challenges of generating evidence for treatments for these rare conditions. These may include challenges to conducting randomized clinical trials, validating surrogate outcome measures, and obtaining long-term efficacy and safety data on a particular therapy. ICER will attempt to produce a cost-effectiveness model for every new treatment that acknowledges and highlights the additional uncertainty in translating patient outcomes into the standard quality-adjusted life-year (QALY) or equal value of life

gained (evLYG) measures. ICER will work to provide willingness-to-pay threshold results per QALY/evLYG over a specific range and will also investigate to find mapping studies that may allow surrogate outcomes to be translated into QOL measurement.²⁶

Applying an Economic Model to LC-FAOD Therapy

Looking at an emerging therapy through such a lens, one can consider triheptanoin. Evaluating this new therapy through the lens of value assessment, triheptanoin is intended to provide patients with medium-length, odd-chain fatty acids that can be metabolized to increase intermediate substrates in the metabolic process. The drug can also be converted to new glucose, providing a potential additional therapeutic effect.²⁷

Considering the early data on the effects of this agent on patient hospitalizations for LC-FAODs noted previously, triheptanoin therapy resulted in a 35% reduction in mean hospitalizations annually, decreasing from 1.94 hospitalizations per year to 1.26; $P = .1126$). There was also a 67% reduction in mean total hospital days annually (5.76 days vs 17.55 days before treatment; $P = .0242$). Hospitalization event rates for rhabdomyolysis changed from 1.05 events annually at baseline to 0.68 events per year after treatment ($P = .4604$) and the hypoglycemia event rate decreased by 96% (0.92 at baseline vs 0.04 following triheptanoin administration; $P = .0091$).⁶

More recent efficacy data exist from an open-label phase 2 study assessing the agent by its impact on the frequency and duration of major clinical events (eg, hospitalizations, emergency department visits, and emergency home visitations for symptoms related to LC-FAODs). Results demonstrated that triheptanoin decreased mean annualized event rates by almost half from 1.69 to 0.88 events per year ($P = .021$), with the mean annualized duration rate decreasing from 5.96 to 2.96 days annually ($P = .028$). Data such as these show the drug's potential benefit in reducing disease burden and direct medical costs associated with symptomatic events. As a result of the efficacy and medical cost offsets, the newly approved product has an annual therapy costing approximately \$138,000 per patient per year.²⁷ It must also be noted that in April 2019, triheptanoin was granted a fast-track designation and rare pediatric disease designation by the FDA for treatment of LC-FAODs, further commenting on the potential overall value of this therapy.²⁸ This fast-track status led to the recent FDA approval of triheptanoin in June 2020.²⁹

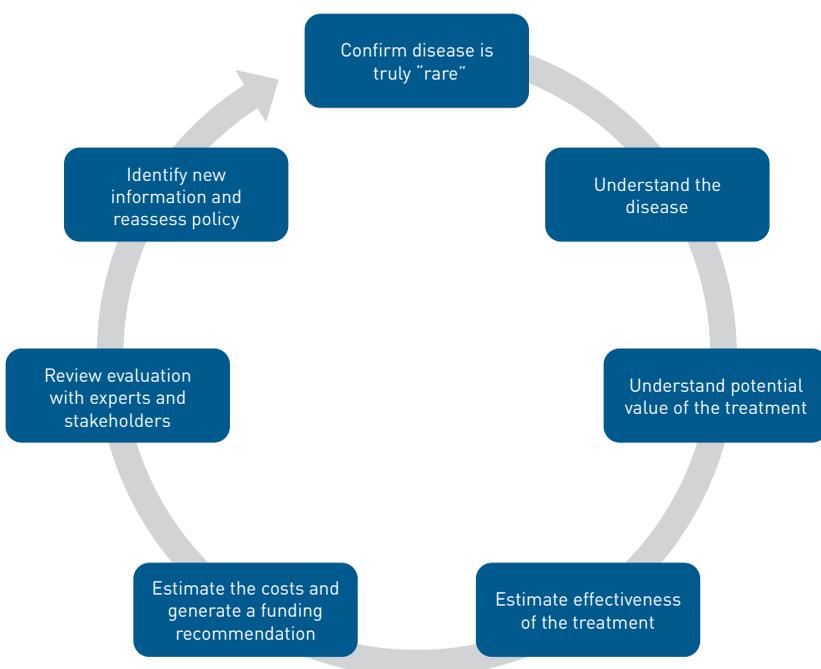
Managed Care Considerations in Treatment of Rare Diseases, Including Emerging Therapies

Managed Care Providers and Patient Population Data

Health plans and payers who can provide information surrounding

patient population data can also provide a more in-depth view into the management of patients with rare diseases. Rare diseases in general take longer to diagnose, incur greater rates of hospitalization, require oversight by both primary care providers and specialists, and usually require a greater volume of diagnostic tests and procedures for optimal management. In addition, rare diseases, especially those with symptoms of variable severity and appearance, may incur substantial healthcare resource utilization, complicated by uncertainty around technologies needed for diagnosis and especially for options surrounding treatment.³⁰⁻³² In a managed care setting, intensive analysis of population health data surrounding a rare disease can help further educate providers to gain a better and more comprehensive understanding of symptoms, treatments, and procedures needed for optimal disease management. A clearer and more complete understanding of risk factors and treatment options for patients with rare diseases will help support health plans in optimizing the overall health of their patient population. Such an inclusive approach and data analysis could

FIGURE. Ontario Policy Framework for Funding Rare-Disease Interventions²³



Adapted from: *Value Health*, Vol. 15/No. 6; Winquist E, Bell CM, Clarke JT, et al, "An evaluation framework for funding drugs for rare diseases," pages 982-986 © 2012, with permission from Elsevier.

improve patient outcomes and even patient QOL while reducing the economic burden associated with rare disease.³⁰

Managed care professionals have several considerations when determining access to orphan drugs. Necessary considerations for new agents in development and their potential future coverage and availability include³³:

- Timing: when will payers be impacted?
- Clinical effectiveness: is this agent better than other available options?
- Patient experience: will this positively or negatively impact patients?
- Payer impact: will this influence prescription spend?

Addressing the High Treatment Costs for Rare Disease in the Managed Care Setting

Managed care providers and organizations continue to debate the best strategies to address the high costs of rare disease treatment to provide optimal care for patients with these conditions. One recent managed care pharmacy survey by the publication *Managed Healthcare Executive* asked managed care consultants, health plans, and pharmacy benefit managers to identify the best long-term approach to managing rare disease costs. Results demonstrated that 28% of participants called for a more integrated health approach by benefit managers surrounding the total cost of care across the healthcare continuum. In addition, 22% of participants called for a National Institute for Health and Care Excellence-based approach or even ICER-based limitations for some therapy access that would center on a measure of cost-benefit (eg, cost or impact on QALY). Data also showed that 19.6% of respondents suggested better assessment of treatment risk versus benefit and discontinuation when clinically appropriate. However, the National Organization for Rare Disorders (NORD) offered cautionary statements on implementing such stringent procedures. Per the vice president of Regulatory and Government Affairs at NORD, the FDA is approving a record number of orphan therapies with a corresponding increase in record prices set for these agents. Utilization management strategies are the cornerstone to controlling overall healthcare costs when multiple brand-name agents, generics, or biosimilar alternatives are available. However, many patients with rare diseases often have just 1 option for treatment. More aggressive utilization management techniques will not work in these circumstances.¹⁹ Recognizing the need for rare disease treatments, managed care organizations have begun expanding medical necessity criteria to go beyond simple physician attestation of disease alone. The shift is to require testing and rigorous documentation to support the diagnosis and confirm the medical necessity of these high-cost therapies. In some instances, organizations have moved to stringent criteria that limit therapy

strictly to p specific patient populations who were studied in clinical trials as opposed to standard FDA-approved indications. The goal of this shift in management approach is to better manage cost by ensuring appropriate utilization in the absence of lower cost alternative therapies.

The Role of the Specialty Pharmacist in Rare Disease Management

The Specialty Pharmacist as Part of the Interprofessional Healthcare Team

Specialty pharmacies play a critical role at the center of pharmaceutical treatments for rare diseases. Often, specialty pharmacies utilize a team of clinicians and administrative staff to manage these patients. Activities include coordination with payers through the authorization process, drug and disease education to patients, and coordination of medication delivery and administration as well as alternative coverage opportunities using patient assistance programs. This can be a period of high anxiety for the patients and those assisting in their care. Having the support from the specialty pharmacy team is critical in ensuring appropriate use of these extremely high-cost medications.³⁴

Specialty pharmacists must work in concert with other members of the multidisciplinary and interprofessional healthcare team to help mitigate the impact of rare diseases in both patients with these disorders as well as their families and caregivers. This type of support requires precise coordination among the patient, caregivers, physicians, specialists, pharmacists, payers, and drug manufacturers. The patient-centered approach that is needed extends well beyond dispensing therapies. Specialty pharmacists must focus on all the fundamentals involved in patient management in rare diseases, especially compassionate and effective communication surrounding the administration and use of the prescribed agent, the nature of the disease itself, and any concomitant patient conditions and comorbidities. Many patients with rare diseases require multiple therapeutic agents, and the treatment regimens to manage their symptoms and prevent or limit adverse effects can be quite complex. The intensive skills of the specialty pharmacist may be needed around the clock to provide the necessary patient and caregiver education and support that enhances patient–prescriber interactions.³⁵

Triheptanoin is supplied as an oral liquid in a 500-mL glass bottle and requires the patient or caregiver to draw appropriate doses and self-administer either orally or enterally. Specialty pharmacists can help clarify administration questions and coordinate with the healthcare team to optimize care. If a patient has difficulty tolerating a quarter of the total dose 4 times daily, the dose can be further reduced and given more frequently. If the patient experiences gastrointestinal adverse effects, the total daily dose can be reduced and more slowly increased back to target. It can

be mixed with semi-solid food or liquids such as plain or artificially sweetened fat-free yogurt, fat-free milk, formula or cottage cheese, whole grain hot cereal, and fat-free low-carbohydrate pudding, smoothies, applesauce or baby food and given orally or through a feeding tube. It should be prepared and administered in compatible containers, syringes, or measuring cups made of stainless steel, glass, high-density polyethylene, polypropylene, low-density polyethylene, polyurethane, and silicone. It should not be administered using plastics made of polystyrene or polyvinyl chloride. Triheptanoin should be thoroughly mixed into the desired food or liquid and can be stored refrigerated for up to 24 hours after being mixed.²⁹

In addition to helping patients with rare diseases with both their general and specific needs, the specialty pharmacist can increase the prescriber's visibility into factors affecting therapy access, adherence, and outcomes by providing actionable updates to improve the overall management pathways.³⁵ Advances in drug development in precision medicine require delicate and careful management, considering the overall costs to patients, payers, and society. In the case of rare diseases, the smaller the patient population affected, the higher likelihood of having a semi-exclusive or exclusive specialty pharmacy dispensing channel, thus allowing better data management, flexibility, and ability to identify and manage therapy results and trends in affected patients.³⁵ As more pharmacies enter the rare disease market, they must put in place the structure and technology to assist every individual patient using these potentially complex therapies. Pharmacy programs will need to incorporate specialized teams with the ability to use program-specific technologies that will lead them through the patient management process and collect and analyze data on the use of these new agents. Overall, pharmacies must develop and implement programs that differ substantially from those for other specialty drugs to provide optimal patient management in the rare disease landscape.³⁶ The specialty pharmacist will be at the center of managing patients and therapies that require high-touch, greater distribution control, and more real-time data. These pharmacists must help channel rare disease treatments to those who need them the most, and in their specialty setting, they are the practitioners most ideally suited to meet this need.³⁵

Conclusions

LC-FAODs are rare diseases, and the symptoms associated with these genetic disorders may result in significant morbidity and mortality, including frequent hospitalizations and even early death. With the potential for a novel agent on the horizon to treat LC-FAODs, new challenges in managing both the clinical and economic burdens of these disorders will arise for managed care decision makers and specialty pharmacists. These healthcare professionals must thoroughly assess emerging agents for therapy in terms of efficacy,

safety, and cost-effectiveness, using evolving algorithms and pathways for determining their optimal use in individual patients. They must also provide appropriate patient and caregiver education on adopting emerging agents into therapy plans in concert with the multidisciplinary and interprofessional healthcare team to optimize patient therapy and improve outcomes in patients with LC-FAODs. □

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Funding source: This activity is supported by an educational grant from Ultragenyx Pharmaceutical Inc.

Author disclosure: Dr Pannier has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to the concept and design; drafting of the manuscript; overall supervision; and critical revision of the manuscript for important intellectual content.

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REFERENCES

- Shekawat PS, Matern D, Strauss AW. Fetal fatty acid oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management. *Pediatr Res*. 2005;57(5 Pt 2):78R-86R. doi: 10.1203/01.PDR.0000159631.63843.3E
- Bennett MJ, Rinaldo P, Strauss AW. Inborn errors of mitochondrial fatty acid oxidation. *Crit Rev Clin Sci*. 2000;37(1):1-44. doi: 10.1080/10408360091174169
- Lindner M, Hoffmann GF, Matern D. Newborn screening for disorders of fatty-acid oxidation: experience and recommendations from an expert meeting. *J Inher Metab Dis*. 2010;33(5):521-526. doi: 10.1007/s10545-010-9076-8
- Conditions screened by state. Baby's First Test. Accessed June 16, 2020. babysfirsttest.org/newborn-screening/states
- Knottnerus SJ, Bleeker JC, Wüst RC, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle. *Rev Endoc Metab Disord*. 2018;19(1):93-106. doi: 10.1007/s11154-018-9448-1
- Vockley J, Marsden D, McCracken E, et al. Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment—a retrospective chart review. *Mol Genet Metab*. 2015;116(1-2):53-60. doi: 10.1016/j.ymgme.2015.06.006
- Baruteau J, Sachs P, Broue P, et al. Clinical and biological features at diagnosis in mitochondrial fatty acid beta-oxidation defects: a French pediatric study of 187 patients. *J Inher Metab Dis*. 2013;36(5):795-803. doi: 10.1007/s10545-012-9542-6
- Lindner M, Gramer G, Haegge G, et al. Efficacy and outcome of expanded newborn screening for metabolic diseases—report of 10 years from south-west Germany. *Orphanet J Rare Dis*. 2011;6:44. doi: 10.1186/1750-1172-6-44
- Bedrosian SJ, Marsden D, Asha S, Kruger E. Mortality associated with long-chain fatty acid oxidation disorders: observations from an expanded access program for triheptanoin. *J Manag Care Pharm*. 2020;26(4-a):S30. Abstract E28.
- Knottnerus SJ, Bleeker JC, Ferdinandusse S, et al. Subclinical effects of long-chain fatty acid β -oxidation deficiency on the adult heart: a case-control magnetic resonance study. *J Inher Metab Dis*. Published online May 28, 2020. doi: 10.1002/jimd.12266
- Knottnerus SJ, Bleeker JC, van Hasselt PM, Wijburg FA, Visser G. Health-related quality of life in patients with long-chain fatty acid oxidation disorders. Published December 26, 2018. Accessed June 16, 2020. informa-network.org/2018/12/26/health-related-quality-of-life-in-patients-with-long-chain-fatty-acid-oxidation-disorders/
- Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab*. 2017;120(4):370-377. doi: 10.1016/j.ymgme.2017.02.005
- Yamada K, Taketani T. Management and diagnosis of mitochondrial fatty acid oxidation disorders: focus on very-long-chain acyl-CoA dehydrogenase deficiency. *J Human Genet*. 2019;46(2):73-85. doi: 10.1038/s10038-018-0527-7
- Siddiq S, Wilson BJ, Graham ID, et al. Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. *Orphanet J Rare Dis*. 2016;11(1):168. doi: 10.1186/s13023-016-0548-2
- Rare diseases by the numbers. America's Biopharmaceutical Companies. Accessed May 20, 2020. innovation.org/about-us/commitment/research-discovery/rare-disease-numbers
- Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: a systematic review of cost of illness evidence. *Health Policy*. 2015;119(7):964-979. doi: 10.1016/j.healthpol.2014.12.016
- Connolly MP, Panda S, Patris J, Hazenberg BP. Estimating the fiscal impact of rare diseases using a public economic framework: a case study applied to hereditary transthyretin-mediated (hATTR) amyloidosis. *Orphanet J Rare Dis*. 2019;14(1):220. doi: 10.1186/s13023-019-1199-x
- Joszt L. Analysis highlights how rare diseases have broader fiscal impact than health costs. *Am J Manag Care*. Published October 15, 2019. Accessed May 21, 2020. ajmc.com/newsroom/analysis-highlights-how-rare-diseases-have-broader-fiscal-impact-than-health-costs
- Sukel K. Balancing the costs of rare disease treatment. *Managed Healthcare Executive*. Published June

- 14, 2019. Accessed May 22, 2020. managedhealthcareexecutive.com/managed-care-pharmacy-survey/balancing-costs-rare-disease-treatment
20. Ollendorf DA, Chapman RH, Pearson SD. Evaluating and valuing drugs for rare conditions: no easy answers. *Value Health*. 2018;12(5):547-552. doi: 10.1016/j.jval.2018.01.008
21. EvaluatePharma world preview 2017, outlook to 2022. Evaluate. Published June 2017. Accessed May 23, 2020. info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf
22. EvaluatePharma Orphan Drug Report 2020. Accessed June 16, 2020. evaluate.com/orphan-drugs
23. Winquist E, Bell CM, Clarke JT, et al. An evaluation framework for funding drugs for rare diseases. *Value Health*. 2012;15(6):982-986. doi: 10.1016/j.jval.2012.06.009
24. Winquist E, Coyle D, Clarke JT, et al. Application of a policy framework for the public funding of drugs for rare diseases. *J Gen Intern Med*. 2014;29(suppl 3):S774-S779. doi: 10.1007/s11606-014-2885-y
25. Blackburn H, Labarthe D. Stories from the evolution of guidelines for causal inference in epidemiologic associations: 1953-1965. *Am J Epidemiol*. 2012;176(12):1071-1077. doi: 10.1093/aje/kws374
26. Modifications to the ICER value assessment framework for treatments of ultra-rare diseases. Institute for Clinical and Economic Review. Updated January 31, 2020. Accessed June 16, 2020. icer-review.org/wp-content/uploads/2020/01/ICER_URD_Framework_Adapt_013120.pdf
27. Vockley J, Burton B, Berry GT, et al. Results from a 78-week, single-arm, open-label phase 2 study to evaluate UX007 in pediatric and adult patients with severe long-chain fatty acid oxidation disorders (LC-FAOD). *J Inher Metab Dis*. 2019;42(1):169-177. doi: 10.1002/jimd.12038
28. Ultragenyx announces UX007 granted Fast Track Designation and Rare Pediatric Disease Designation by U.S. FDA for treatment of long-chain fatty acid oxidation disorders. News release. Intrado GlobeNewswire; April 16, 2019. Accessed May 24, 2020. globenewswire.com/news-release/2019/04/16/1804740/0/en/Ultragenyx-Announces-UX007-Granted-Fast-Track-Designation-and-Rare-Pediatric-Disease-Designation-by-U-S-FDA-for-Treatment-of-Long-Chain-Fatty-Acid-Oxidation-Disorders.html
29. Dojolvi. Prescribing information. Ultragenyx Pharmaceutical Inc; 2020. Accessed July 15, 2020. ultragenyx.com/medicines/dojolvi-full-prescribing-information
30. Johnson MP, Johnson JC, Engel-Nitz NM, et al. Management of a rare disease population: a model for identifying a patient population with tuberous sclerosis complex. *Managed Care Magazine*. Published August 28, 2017. Accessed May 24, 2020. managedcaremag.com/archives/2017/8/management-rare-disease-population-model-identifying-patient-population-tuberous
31. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. *Lancet*. 2008;371(9629):2039-2041. doi: 10.1016/S0140-6736(08)60872-7
32. de Vroeh R, Baekelandt ER, de Haan JM. Priority Medicines for Europe and the World: "A Public Health Approach to Innovation." Update on 2004 Background Paper. Background Paper 6.19 Rare Diseases. World Health Organization; March 12, 2013. Accessed May 24, 2020. who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf
33. Orphan drug debate: understanding the increasingly popular and competitive orphan drug market while balancing this costly trend. EnvisionRx. Published July 19, 2018. Accessed May 24, 2020. visibly-different.envisionrx.com/blog/perspective-on-the-rx-pipeline-orphan-drugs
34. Boutwell L. Ask the pharmacist: after a rare disease diagnosis, what's next? Express Scripts. Published February 26, 2020. Accessed May 25, 2020. express-scripts.com/corporate/articles/ask-pharmacist-after-rare-disease-diagnosis-whats-next
35. Suket K. Specialty pharmacy's role in improving orphan drug channels. *Managed Healthcare Executive*. Published May 3, 2019. Accessed July 21, 2020. managedhealthcareexecutive.com/view/specialty-pharmacies-role-improving-orphan-drug-channels
36. Rare pharmacy emerges from specialty (pharmacy). PANTHERx Rare Pharmacy. Published May 4, 2020. Accessed June 17, 2020. pantherxrare.com/blog/white-paper-rare-pharmacy-emerges-from-specialty-pharmacy-published

The Challenges in Long-Chain Fatty Acid Oxidation Disorders: Unmet Needs of Treatment and Management

Release date: August 14, 2020

Expiration date: August 14, 2021

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which of the following are clinical manifestations related to long-chain fatty acid oxidation disorders (LC-FAODs)?
 - A. Cardiomyopathy and hyperglycemia
 - B. Cardiomyopathy and diabetes
 - C. Hyponatremia and hyperammonemia
 - D. Hypoketotic hypoglycemia and rhabdomyolysis
2. LC-FAODs are inborn errors of metabolism due to a disruption of fatty acid substrates into which part of the cell structure?
 - A. Golgi apparatus
 - B. Mitochondria
 - C. Nucleus
 - D. Ribosomes
3. Parents/caregivers of chronically ill children who are at a greater risk of a lower health-related quality of life often experience which of the following issues?
 - A. Posttraumatic stress
 - B. Neuropathy
 - C. Insomnia
 - D. Myocardial infarction
4. When using even medium-chain triglyceride (MCT) oil, it is important that patients do not exceed:
 - A. 2-3 tablespoons per day
 - B. 3-5 tablespoons per day
 - C. 4-7 tablespoons per day
 - D. 5-8 tablespoons per day
5. Which of the following correctly describes the properties of triheptanoin?
 - A. It is an odd-chain fatty acid that can directly enter the mitochondria where it is metabolized into acetyl-CoA and anaplerotic propionyl-CoA.
 - B. It is an odd-chain fatty acid that requires a carnitine shuttle to enter the mitochondria where it is metabolized into acetyl-CoA.
 - C. It is an even-chain fatty acid that can directly enter the mitochondria where it is metabolized into acetyl-CoA and cataplerotic propionyl-CoA.
 - D. It is an even-chain fatty acid that requires a carnitine shuttle to enter the mitochondria where it is metabolized into acetyl-CoA and anaplerotic propionyl-CoA.
6. Which of the following is a common adverse effect associated with triheptanoin administration?
 - A. Abdominal pain
 - B. Constipation
 - C. Headache
 - D. Hyperglycemia
7. An 18-year-old girl who received a diagnosis of LC-FAOD presents with increasingly recurrent gastrointestinal (GI) issues including abdominal discomfort, bloating, and diarrhea. During clinical assessment, it is revealed that the patient has been taking the total daily dose of MCT oil at breakfast. What recommendation can be suggested to reduce or alleviate her GI issues?
 - A. Discontinue MCT oil
 - B. Supplement with carnitine
 - C. Take MCT oil on empty stomach
 - D. Equally divide the daily dosage of MCT oil among all meals during the day

8. A newborn male child has been diagnosed with an LC-FAOD. What is the estimated rate for substantial decompensation in terms of his illness in his first 2 years of life?
- A. 15%
 - B. 20%
 - C. 25%
 - D. 30%
9. Per current estimates, what is the approximate monetary value predicted for sales of orphan drugs in 2024?
- A. \$167 billion
 - B. \$217 billion
 - C. \$267 billion
 - D. \$317 billion
10. In the *Managed Healthcare Executive* managed care pharmacy survey on rare diseases, what percentage of participants requested a more integrated approach by benefit managers surrounding the total cost of care across the healthcare continuum?
- A. 18%
 - B. 23%
 - C. 28%
 - D. 33%

