

Achieving High-Quality Patient Outcomes in Spinal Muscular Atrophy: A Review of New Data and Managed Care Strategies

HIGHLIGHTS

- › Updates in Clinical Data for FDA-approved Disease-modifying Therapies for Spinal Muscular Atrophy
- › Spinal Muscular Atrophy: An Update for Managed Care Pharmacists
- › CE Sample Posttest

Achieving High-Quality Patient Outcomes in Spinal Muscular Atrophy: A Review of New Data and Managed Care Strategies

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Pharmacists and managed care professionals

Activity Overview

It is estimated that about one in 65 people are carriers of the gene mutation for spinal muscular atrophy (SMA), which causes degeneration of motor neurons and progressive muscle weakness affecting patients' ability to move, swallow, and breathe. The rapid progression of SMA and high rate of mortality have contributed to its designation as a recommended condition for which all newborns should receive screening. The majority of patients with SMA present with signs and symptoms by 3 months of age, but symptom onset can vary according to SMA type, thus affecting treatment decisions and making early diagnosis and treatment initiation imperative. Previously, management of SMA consisted primarily of supportive care with specialized equipment, such as ventilators and feeding tubes, physical and occupational therapy, and other expert care to maintain patient quality of life, with astronomical associated costs. However, use of disease-modifying therapies has the potential to change existing treatment protocols, normalize development, and increase survival, especially for patients in whom a diagnosis was received early. These therapies are also associated with high costs and are often subject to extensive barriers to access. To balance the costs of treatment with improvement of patient outcomes, managed care professionals and pharmacists must establish a framework for evaluating newly approved therapies and expediting the use of these agents in the treatment of SMA.

Statement of Educational Need

Recent drug approvals for the treatment of spinal muscular atrophy (SMA) have prompted the development of treatment guidelines along with recommendations for genetic testing for diagnosis. Due to the rarity of SMA, and the historical lack of pharmacotherapy, managed care pharmacists may not have exposure to this highly morbid disease state and medications. Cost of treatment must be considered, and managed care pharmacists need to be provided with the appropriate tools to make the best evidence-based formulary decisions and develop appropriate utilization management strategies.

Educational Objectives

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

- Determine gold standards for treating spinal muscular atrophy (SMA) including updates to the 2020 revised recommendations.
- Use the most up-to-date clinical data of approved therapies to aid in advancing treatment options and patient-specific protocols for SMA.
- Employ strategies that allow access to patient-specific treatment protocols and the potential opportunities to offset costs in SMA.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge of disease-modifying therapies for the treatment of spinal muscular atrophy

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COPY & PRODUCTION

Copy Chief

Jennifer Potash

Copy Supervisors

Rachelle Laliberte
Paul Silverman

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Circulation Director

Jon Severn
circulation@mjhassoc.com

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FACULTY

Elizabeth Bisaccia, PharmD, BCPPS

Clinical Pharmacy Specialist
Rush University Medical Center
Chicago, Illinois

Alan D. Pannier, PharmD, MBA

Head of Clinical Services
SmithRx
Salt Lake City, Utah

MEDICAL WRITING & EDITORIAL SUPPORT

Brittany Hoffmann-Eubanks, PharmD, MBA

Founder and CEO
Banner Medical LLC
Frankfort, Illinois

Andrew Abe, PharmD

Medical Writer
Honolulu, Hawaii

FACULTY DISCLOSURES

Elizabeth Bisaccia, PharmD, BCPPS, and **Alan Pannier, PharmD, MBA,** have no

relevant financial relationships with commercial interests to disclose.

MEDICAL WRITING & EDITORIAL SUPPORT DISCLOSURES

Brittany Hoffmann-Eubanks, PharmD, MBA,

and **Andrew Abe, PharmD,** have no relevant financial relationships with commercial interests to disclose.

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Updates in Clinical Data for FDA-approved Disease-modifying Therapies for Spinal Muscular Atrophy

Elizabeth Bisaccia, PharmD, BCPPS

Introduction

Spinal muscular atrophy (SMA) describes a diverse group of inherited neuromuscular disorders characterized by degradation of the lower motor neurons causing progressive muscle atrophy and weakness. Although SMA results in neuromuscular degeneration, it does not affect neurocognitive ability.^{1,2} The most common form of SMA (about 95% of cases) occurs due to a homozygous deletion (less frequently a point mutation) located on the 5q13 region of the survival motor neuron 1 (*SMN1*) gene.^{1,3-8} The *SMN1* gene is responsible for encoding SMN1 protein, ensuring alpha motor neuron fibers' survival.³ The *SMN2* gene is closely related to *SMN1*, but produces less protein than *SMN1*.⁹ The *SMN2* gene still produces enough protein that the clinical severity of SMA is dictated by the number of *SMN2* copies an affected individual with SMA has. The fewer the copies of *SMN2*, the more severe the SMA phenotype.¹⁰ Some forms of SMA are fatal without treatment, and patients diagnosed with the most severe form of disease will die of respiratory failure by 2 years of age unless they are provided continuous mechanical ventilation.^{9,11}

SMA affects approximately 10,000 to 25,000 children and adults within the United States, making SMA the most common fatal genetic disease among infants.^{1,12} The estimated incidence of SMA is 1 in 6000 to 11,000 live births, and a 1 to 2 per 100,000 individual prevalence.^{1,2,13,14} Due to disease rarity and inconsistent newborn screening across the United States, these numbers have been difficult to ascertain. The first newborn studies conducted within the United States suggest a 1:40 SMA carrier frequency; however, reported frequencies vary based on ethnicity (1:48-1:97).

Over the past few years, significant changes have occurred with the licensing of disease-modifying therapies (DMTs) for the treatment of SMA. The medical management of patients with SMA has drastically evolved, along with the affected patient's quality of life, survival outcomes, and parent and/or caregiver burden. Three agents are now commercially available within the United States, and pharmacists must have a thorough understanding of these therapies' efficacy and safety data to help the SMA care team, patients, and caregivers obtain the best benefit from these

ABSTRACT

Spinal muscular atrophy (SMA) is a rare, diverse group of inherited neuromuscular disorders that cause degradation of the lower motor neurons, progressive muscle atrophy, and weakness. The natural history of SMA has changed significantly with an increased understanding of SMA pathophysiology and new technologies. As a result, affected individuals now have 3 disease-modifying therapies available for treatment. Evidence suggests that these novel agents are more effective when started early in the disease process. This reinforces the importance of newborn screening as a mechanism for early diagnosis. Pharmacists are highly valued members of the healthcare team who play a pivotal role in the SMA care team. Therefore, pharmacists must be up-to-date on SMA's medical management, including the most current efficacy and safety data to assist providers, caregivers, and patients in selecting these agents and ensuring patients with SMA receive optimal and timely medical care.

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For author information and disclosures, see end of text.

therapies. Therefore, the purpose of this educational activity is to update pharmacists on the management of SMA, including classification, diagnosis, and screening. This activity will also review the most recent SMA standards of care, outcome measures, and safety and efficacy data for nusinersen, onasemnogene abeparvovec, and risdiplam.

Classification, Diagnosis, and Screening of SMA

SMA Classification

The clinical burden of SMA is highly variable. Historically, SMA was classified into 3 subtypes dependent on the affected individuals' age of onset and highest achieved motor function (Werdnig Hoffmann disease [type 1], Dubowitz syndrome [type 2], and Kugelberg Welander disease [type 3]) outlined in **Table 1**.² The classification system would then expand further (Table 1²) to include congenital- or prenatal-onset (type 0, type 1 in later classifications) and adult-onset (type 4).¹⁵⁻¹⁸ However, the natural history of SMA has evolved significantly with additional clinical trials and the development of therapeutics resulting in previous classification systems

becoming less practical.¹⁵ Treated SMA is now considered to lie on a continuum because patients frequently gain motor function versus progressive loss among those untreated. To address these changes, updates to the classification system categorize individuals with SMA as nonsitters, sitters, and walkers while focusing on current functional status and treatment response (**Table 2**).^{15,19-26}

SMA Diagnosis and Screening

In the past, SMA was diagnosed once clinical signs appeared (such as proximal muscle weakness, motor delay, or regression).²¹ Now, if there is a high clinical suspicion of SMA, diagnosis occurs with genetic testing that may include multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR), or next-generation sequencing (NGS).²¹

An individual must be missing both functional *SMN1* copies to be diagnosed with SMA.²¹ If one functional *SMN1* copy is present, additional testing should occur to determine if other mutations are present. Furthermore, if an individual has 2 functional *SMN1* copies but has a strikingly typical SMA phenotype, additional

TABLE 1. Historical Phenotypes of Spinal Muscular Atrophy²

Phenotype	Number of SMN2 copies	Alternative name	Age of onset	Natural age of death
0	-	-	Prenatal/birth	<6 months
1	2	Werdnig Hoffmann disease	<6 months	<2 years
2	3	Dubowitz syndrome	6-18 months	>2 years
3	3	Kugelberg Welander disease	>18 months	Adulthood
4	4-6	Adult-onset	Adult ^a	Adult

^aUsually in 2nd or 3rd decade of life.

Adapted with minimal changes from Verhaart IE, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy – a literature review. *Orphanet J Rare Dis.* 2017;12(1):124, under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

TABLE 2. New Proposed SMA Classification and Common Clinical Features^{15,19-26}

Proposed SMA classification	SMA patient population	Common clinical features	Notes
Nonsitters	Majority of SMA type 1	<ul style="list-style-type: none"> Bulbar musculature impairing swallowing and secretion management Bell-shaped thorax deformity Frog-leg posture (supine), poor head control 	<ul style="list-style-type: none"> Some independent sitters with SMA type 2 can revert back to nonsitters^a Nutrition/respiratory support helped decrease mortality
Sitters	SMA type 2 and type 3 ^b	<ul style="list-style-type: none"> Can sit independently, unable to walk or stand independently^c Joint contractures, mandible ankyloses, scoliosis 	<ul style="list-style-type: none"> Scoliosis plus weak intercostal muscles can lead to restrictive lung disease with respiratory insufficiency Survival outcomes dictated by level of respiratory challenges
Walkers	SMA type 3 or type 4	<ul style="list-style-type: none"> Have and maintain ability to ambulate More severe cases may include scoliosis and respiratory insufficiency 	<ul style="list-style-type: none"> Ability to ambulate is correlated with age of onset/independent sitting

SMA, spinal muscular atrophy.

^aDisease onset after 6 months of age.

^bSMA type 3 whose weakness has progressed to non-ambulatory.

^cOr lost the ability.

genetic testing should occur to assess for rarer forms of SMA (or neuromuscular disorders) other than 5q SMA.²¹

An SMA diagnosis is commonly delayed for most people and can range between 4 months after symptom onset (SMA type 1) to greater than 10 months, or sometimes years, among people with SMA type 3.²⁷⁻²⁹ Per and colleagues followed 5 Italian centers and examined the limitations that led to delays in diagnosis.³⁰ What the investigators found was that the mean time between symptom onset and diagnosis in patients with type 1 was 1.94 months, in type 2 it was 5.28 months, and in type 3 it was 16.8 months. Much of the delay in diagnosis is attributed to the age at which patients would present with symptoms based on disease severity and reinforced the importance of newborn screening as a mechanism for early diagnosis. In patients with delayed diagnosis, initiation of DMTs may not be as effective because significant degeneration of the non-regenerable alpha motor neurons has already occurred.³⁰

Therefore, a greater emphasis on prenatal carrier testing and newborn SMA genetic screening has resulted in the hopes of identifying infants with SMA earlier so DMTs can be initiated sooner. In the United States, the federal Recommended Uniform Screening Panel added SMA in 2018, with 33 states currently adopting and implementing the recommendation (a full list of all states may be found at www.curesma.org/newborn-screening-for-sma/).³¹

Biomarkers are also another tool being investigated to help identify patients with SMA sooner, predict disease severity, and optimize therapy. More than 200 candidates exist focusing on *SMN2* copy number and/or non-SMN-related biomarkers. A review of biomarkers is beyond the scope of this document but was recently reviewed by Kariyawasam et al.³²

SMA Standards of Care and Scoring Tools

SMA Standards of Care

The 2018 SMA Standards of Care emphasize the importance of a multidisciplinary approach for the management of patients with SMA.^{20,21} SMA is a highly complex disorder that requires multiple specialties (eg, neurology, orthopedics, respiratory, nutrition and gastrointestinal, pharmacy) work in concert along with a coordinator and the patient's family to provide the best possible outcomes for the affected patient.²¹

Before the approval of pharmacologic therapies, supportive care was the only option for patients with SMA, especially respiratory care as these patients will eventually progress to requiring ventilation. Airway clearance that consists of manual chest physiotherapy plus mechanical insufflation-exsufflation should be the primary methods used in patients who are ambulatory.^{20,21} Airway clearance measures must be implemented proactively based on a physical assessment to manage respiratory illnesses aggressively. Clinical assessment should include cough effectiveness, nocturnal hypoventilation, and any potential for infection among ambulatory

individuals.³³ Nutritional support in patients diagnosed with SMA has also been a historically important component of care. Hurst Davis et al published survey results in which all patients with SMA type I were found to require nutritional support via feeding tube, elemental formulas, probiotics, and bowel regimens.³⁴ Orthopedic professionals will often be involved in the management of these patients due to progressive spinal deformities. These specialists may provide braces as palliation for spinal curvature and often perform surgical interventions to correct deformities.²¹ As stated previously, care of patients with SMA should be multidisciplinary and include other healthcare providers as required to ensure patients receive a comprehensive treatment plan.³³

As more research has been conducted and SMA pathology is better understood, it has become clear that early treatment is critical to preventing the rapid and progressive nerve degeneration seen in SMA.²⁷ For example, evidence suggests that more than 90% of motor units are lost within the first 6 months of age among patients with SMA type 1. Thus, as SMA still has a diagnostic delay and newborn screenings are not available everywhere within the United States, the optimal window for therapeutic intervention may be missed in many patients because treatment options can only be evaluated once the diagnosis has been made.²⁷

In 2018, Glascock et al released a treatment algorithm developed for infants identified as SMA-positive via newborn screening based on their *SMN2* copy number.²⁷ The working group developed this algorithm to identify which patients should be treated immediately following a positive newborn screen.²⁷ SMA is a disease state with a wide range of severity and acuity. Some manifestations of the disease are imminently life threatening, whereas others, while rare, may be completely asymptomatic. The working group that designed the algorithm consisted of 15 SMA experts who used a modified Delphi process moderated by a neutral third-party expert. Glascock et al recommended that infants with 2 or 3 copies of *SMN2* should receive immediate treatment. Infants with 1 copy were recommended to be treated if they were truly pre-symptomatic, and if they had symptoms, it was up to the physician's discretion. Similarly, among patients with 4 or more copies of *SMN2*, the working group recommended to monitor and begin treatment at the onset of symptoms. Also, routine follow-up care should occur every 3 to 6 months until the patient is 2 years old, and every 6 to 12 months after treatment if not started immediately. The working group also recommended follow-up tests such as electromyography, compound muscle action potential monitoring, myometry, physical examinations, and motor function scales in patients once they achieve the appropriate age.²⁷ Finally, parents and/or caregivers should be educated to notify their primary SMA healthcare provider if they observe a significant change in their child (eg, movement, feeding, breathing pattern, increased fatigue, voice/cry changes).³⁵

In 2019, the SMA working group reconvened and determined sufficient new clinical data and real-world experience existed to justify reevaluating infants with 4 copies of *SMN2* who were confirmed SMA-positive via newborn screening.³⁶ Glascock et al updated their position, whereby, they now recommend immediate treatment for infants diagnosed with SMA from newborn screening with 4 copies of *SMN2*. In addition, the working group reaffirmed their recommendation for watchful waiting among infants with 5 *SMN2* copies. All other recommendations remained the same as outlined in the previous 2018 treatment algorithm.^{27,36}

SMA Outcome Measures

Historically, SMA muscle weakness was measured directly via assessments of strength, and those data were used to describe the level of impairment or disease severity experienced by affected patients.³⁷ Today, outcome measures in SMA focus on the patient's functional status and quality of life. Measurement tools that evaluate how well individuals with SMA function in their daily lives are considered more clinically relevant and meaningful. Furthermore, changes in strength can be evaluated more appropriately to assess how the change will impact a patient's performance. Early tests such as the Test of Infant Motor Performance had good reliability but were poorly tolerated in patients with SMA type 1 due to the patient needing to be in the prone position, which taxed the respiratory reserve because of diaphragmatic breathing.³⁸

With the promise of pharmacologic therapies on the horizon, SMA experts worldwide coalesced to develop and validate outcome measures that could be used for surrogate end points in clinical practice and clinical trials.³⁷ Five of the most common outcome measures used in SMA research and clinical practice are outlined in more detail below.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

CHOP INTEND is a validated 16-item scale developed to evaluate motor function in infants with SMA type 1.^{38,39} The tool was developed based on the natural history progression of motor function.³⁷ The 16 items are graded on a scale of 0 (no response) to 4 (complete response) and are ordered to minimize position changes, the prone position, and purposely test least tolerated items last. The CHOP INTEND test takes approximately 15 to 40 minutes based on how cooperative the infant/child is. The maximum test score is 64.

Based on research using the CHOP INTEND scoring tool, children with SMA who are untreated have declining scores over time.³⁷ Further, infants with SMA have significantly lower CHOP INTEND scores compared with age-matched typically developing infants over the same time.^{40,41} Infants with SMA type 1 who possess 2 copies of *SMN2* have an average score of 20.2 and do not score above 36.³⁷ Results of long-term data showed a mean change in the loss of -0.31

points/month (mild to severe phenotypes), -0.04 points/month (mild phenotypes), and -12.67 points over 2 years.⁴¹⁻⁴³ The CHOP INTEND scoring tool was created to optimize the measurement of motor skills in the SMA patient population; however, further studies will be needed to continue to establish validity of this tool and quantify the sensitivity of this test to accurately measure change over time.³⁹

Hammersmith Infant Neurological Examination-Section 2, Motor Milestones (HINE-2)

HINE-2 is a motor function assessment tool developed to evaluate infants' motor skills and can be used to assess patients aged 2 to 24 months diagnosed with SMA. Section 2 of the HINE motor milestones is a brief (5-15 minute), standardized assessment tool that evaluates 8 motor skills (voluntary grasp, ability to kick, head control, sitting, crawling, standing, rolling, and walking) and their progression in healthy or high-risk infants. The milestone progression score shows increased levels of functional ability moving from left to right. The total score is the sum of points from each functional item and ranges from 0 to 26.

Despite HINE-2 not being designed for individuals with SMA specifically, it has been used in SMA clinical trials and was found to be both reliable and sensitive to change.³⁷ HINE-2 was capable of detecting change over time in 16/19 infants with type 1 SMA (in all 8 motor skill domains).⁴⁴ Improvements observed in HINE-2 were likewise correlated with changes in other neuromuscular outcome measures.⁴⁴

Hammersmith Functional Motor Scale-Expanded (HFMSE)

The HFMSE scale is used to assess children's (aged >24 months) ability to perform multiple activities in later-onset SMA types 2 and 3. The HFMSE scale contains 33 items, and increased functional ability moves from left to right. The maximum score is 66, with each item being scored from 0 to 2. It is recommended that the HFMSE is performed by a healthcare provider experienced in handling children and adults with SMA. The test takes approximately 10 to 30 minutes to complete. The HFMSE scale is highly correlated with the gross motor function measure and can help healthcare providers determine the SMA type and ambulatory and respiratory function.³⁹

Revised Upper Limb Module (RULM)

The RULM scale assesses upper limb function among ambulatory and non-ambulatory children and adults with SMA.³⁷ Both upper limbs should be measured and scored using the 19-item test. Items assessed are typically associated with activities of daily living such as pressing a button, placing hands on lap, and picking up a token.^{45,46} RULM has a maximum score of 37, with each item being scored from 0 to 2 (one item scored as can or cannot). The test requires 10 to 15 minutes to complete.³⁷

6-Minute Walk Test (6MWT)

The 6MWT is an objective measure of functional exercise capacity among ambulatory individuals with later-onset SMA.³⁷ The 6MWT measures how far an individual can walk in 6 minutes on a linear 25-meter marked course. The test takes approximately 10 minutes to complete and has demonstrated excellent reliability and convergent validity in patients with SMA.³⁷

Bayley Scales of Infant Development (BSID-III)

The Bayley Scales of Infant Development (BSID) are now on their third iteration.⁴⁷ The original BSID was developed out of the National Collaborative Perinatal Project and served as an important standard for the assessment of infant and toddler development between age 2 and 30 months. Now in its third edition, this scale assesses the development of infants and toddlers aged between 1 and 42 months. This assessment is completed both by observation and a caregiver questionnaire. Sections of this assessment include evaluation of behavior, language, and fine motor and gross motor development.⁴⁷ Within the motor scale, patients will complete tasks such as grasping, stacking blocks, sitting, and climbing stairs. Items on this scale are scored as able or unable. Currently, there are no data to support use of the BSID-III specifically in the SMA population.³⁷

Motor Function Measure-32 (MFM-32)

MFM-32 is an assessment comprising 32 tasks across 3 dimensions to assess a patient's motor abilities.⁴⁸ Dimension 1 assesses standing and transfers. Dimension 2 assesses axial and proximal motor function. Dimension 3 assesses distal motor function. Patients are scored based on a 4-point scale in which 0 means they cannot initiate the task or maintain a starting position and 3 indicates that the patient can complete the task fully and completely. Upon completion of the scoring tool, the lower a patient score, the more severe the motor impairment.⁴⁸

SMA Treatment

Nusinersen

Nusinersen is an antisense oligonucleotide that causes pre-messenger RNA (mRNA) splicing of the *SMN2* gene to increase exon 7 inclusion in *SMN2* mRNA transcripts, increasing production of full-length *SMN* protein.^{3,49} Nusinersen was approved by the FDA in 2016, making it the first disease-specific therapy for SMA.⁴⁹ Nusinersen is indicated for the treatment of SMA in pediatric and adult patients based on results from 2 pivotal phase 3 randomized, double-blind, sham-controlled trials (ENDEAR and CHERISH).^{50,51} Both phase 3 trials were terminated early due to statistically and clinically significant differences demonstrated during an interim analysis of the nusinersen and control groups.^{50,51}

Nusinersen is administered to patients intrathecally.⁴⁹ Each dose of nusinersen is 12 mg (5 mL). When patients are initiated

on therapy, they must complete a series of loading doses before moving on to maintenance therapy. The first 3 loading doses of nusinersen are administered every 14 days. The fourth and final loading dose of nusinersen is administered 30 days after the third dose. After completing the loading dose regimen, patients are started on maintenance therapy that includes 1 intrathecal injection every 4 months. Nusinersen is approved in pediatric and adult patients with SMA.⁴⁹

ENDEAR (NCT02193074) evaluated the safety and efficacy of intrathecal nusinersen in 121 infants with infantile-onset SMA who were aged 6 months or younger.⁵⁰ The primary efficacy end points included motor-milestone response, defined according to HINE, and event-free survival. An interim analysis showed that patients treated with nusinersen had higher HINE motor milestone improvement (41%) compared with the control group (0%) ($P < .001$). The nusinersen group had a prolonged time to death (hazard ratio for death, 0.37; $P = .004$) or need for permanent ventilation compared with controls. Also, 8.2% (6/73) of nusinersen-treated patients could sit independently, and those with shorter disease duration had an improved response to treatment.⁵⁰ Due to the overwhelming evidence of efficacy, ENDEAR was terminated early, and all patients were enrolled in the open-label extension study SHINE (NCT02594124) to further evaluate the long-term safety and tolerability of nusinersen in patients with SMA who previously participated in ENDEAR and CHERISH.^{20,52} Results of the final analysis of ENDEAR showed 51% of nusinersen-treated infants had a motor-milestone response compared with 0% in the control group. The nusinersen-treated infants also had a 47% lower risk of death or use of permanent assisted ventilation (hazard ratio, 0.53; 95% CI, 0.32–0.89; $P = .005$).⁵⁰

CHERISH (NCT02292537) included 126 children with later-onset SMA defined as symptom onset after 6 months of age (age range, 2–9 years).⁵¹ The primary end point was the least-squares mean change from baseline in the HFMSE score at 15 months of treatment.⁵¹ Interim analysis showed that the nusinersen group had a mean 4-point increase versus a 1.9 mean decrease in the controls ($P < .001$) in the HFMSE score. A least-squares mean increase of 4.2 points in the nusinersen (–0.5 points in the control group) from baseline to 15 months using RULM score ($P < .001$) was also seen. The final analysis showed that 57% of patients treated with nusinersen compared with 26% in the sham group had a 3-point rise in HFMSE scores after 15 months of treatment. Like ENDEAR, the CHERISH trial was also terminated early based on these positive results, and all patients were enrolled in the SHINE trial. Moreover, this trial also demonstrated the capacity of nusinersen to effect positive meaningful changes on the clinical course of SMA among children with later-onset SMA.⁵¹

The SHINE open-label extension trial began in November 2015 and has an estimated completion date of August 2023. All patients

enrolled in SHINE were moved to 12-mg intrathecal injections every 4 months. Data up to the October 2018 cutoff date showed 89 children moved from ENDEAR to SHINE from the nusinersen group and 24 from the control group.⁵³ Among the children who originally received nusinersen in ENDEAR, 36% could sit without support, 8% could stand with assistance, and 5% were able to walk with assistance compared with 0% who received placebo in ENDEAR. The abstract did not include data from the 2019 cutoff; however, it is noted by the manufacturer that individuals who began nusinersen earlier in the disease process had the greatest benefit compared with those who started later and only had evidence of motor function stabilization or improvement.⁵³ Similarly, CHERISH had 83 nusinersen and 42 placebo patients that transitioned to SHINE.⁵⁴ Again, patients who were started earlier on nusinersen had better motor function evaluated using the HFMSE and RULM scores compared with the control group in CHERISH.⁵⁴ Results from 5 young adults with SMA types 2 and 3 who began nusinersen treatment between the ages of 13 and 15 in the CS2 trial and open-label CS12 who moved to SHINE were also reported.⁵⁵ Data using a 2018 cutoff found 3 patients who were able to ambulate were still able to throughout SHINE, and 1 non-ambulatory patient was able to stand with assistance, and the final patient was able to sit without support during SHINE.⁵⁵

Nusinersen is also being evaluated in NURTURE (NCT02386553), an open-label interventional study assessing the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of intrathecal nusinersen in genetically diagnosed pre-symptomatic infants aged 6 weeks or younger (at first dose) with SMA.⁵⁶ The primary end point is time to death or respiratory intervention. Interim results from 25 infants found that four met the primary end point (ie, required respiratory support during a time of illness). All infants could sit without support, 22 were able to walk unassisted, and 17 could walk independently. These data emphasized the importance of newborn screening and early treatment as soon as a genetic diagnosis is made in pre-symptomatic infants.⁵⁶ In June 2020, new NURTURE data (as of February 2020) reported that all 25 patients (median age, 3.8 years) treated with nusinersen were alive and did not require permanent ventilation.⁵⁷ A notable finding as most children with SMA type 1 who are untreated rarely live to age 2 years. All children who achieved walking independently have maintained that ability from the first occurrence through their last visit. The study has been extended an additional 3 years to evaluate the participants through age 8 years and collect longer-term efficacy and safety data.⁵⁴ The new estimated study completion date is set for February 2025.⁵⁸

In March 2020, research of nusinersen was continued with a phase 2/3 controlled dose-escalating trial, DEVOTE (NCT04089566).⁵⁹ The purpose of the DEVOTE study is to evaluate whether a higher dose of nusinersen will increase treatment efficacy (using CHOP INTEND) across a broad group of patients with SMA (including adults). The trial will be completed in 3 parts and include an open-label safety

evaluation and a pivotal, double-blind, active-control randomized treatment period followed by an open-label treatment period. After the safety evaluation, 2 loading doses of 50 mg administered 14 days apart, followed by a maintenance dose of 28 mg every 4 months, will be evaluated.⁶⁰ The third part of the trial will determine how to safely and efficiently transition patients from the current FDA-approved dosing to the higher nusinersen dose evaluated in the study. The study has an estimated study completion date of July 4, 2023.⁵⁹

In July 2020, plans for a phase 4 trial, RESPOND, were announced to evaluate the benefit of nusinersen in infants and children treated with onasemnogene abeparvovec with unmet clinical needs after treatment.⁶¹ RESPOND will be a 2-year, open-label study that will evaluate change from baseline on motor function measures, other clinical outcomes, and caregiver burden. This trial will also use an exploratory biomarker end point (neurofilament levels) for biological disease activity. The trial estimates to enroll 40 infants aged 9 months or younger with 2 copies of *SMN2* who received onasemnogene abeparvovec at 6 months of age or younger. The second study group will include 20 children and evaluate nusinersen in children up to 3 years old at the first time of nusinersen dose. The RESPOND trial sponsors expect to begin enrolling in the first quarter of 2021.⁶¹

Onasemnogene abeparvovec

Onasemnogene abeparvovec is an adeno-associated virus type 9 (AAV9) vector-based *SMN1* gene therapy that replaces the *SMN1* gene encoding human SMN protein.⁶² Onasemnogene was FDA approved in May 2019 for the treatment of SMA in pediatric patients younger than 2 years with bi-allelic mutations in the *SMN1* gene.⁶² Approval for this agent was granted based on a completed phase 1 and an ongoing phase 3 clinical trial in infantile-onset SMA. The FDA-approved dosing for onasemnogene is 1.1×10^{14} vector genomes per kilogram of patient's body weight. Onasemnogene is administered as an intravenous infusion over 60 minutes.⁶²

The START phase 1 trial (NCT02122952) included 15 infants with SMA type 1 who had 2 copies of *SMN2* in a single-arm, open-label, ascending-dose study.⁶³ The purpose of the study was to evaluate the preliminary efficacy and safety of onasemnogene.⁶⁴ Safety was the study's primary outcome (defined as any treatment-related adverse effects, grade 3 or higher), and time until death or the need for permanent ventilation was the secondary outcome. An amendment to the study protocol was made after an elevated serum aminotransferase occurred in the first patient (cohort 1) to administer concomitant oral prednisolone. At 2 years post-infusion, 1 participant in the low-dose cohort met the end point of permanent ventilation, but the ventilation requirement was reduced by 25%, and all patients in the high-dose cohort were free from permanent ventilation. Also, 9 of 12 participants (75%) in the high-dose cohort could sit independently for more than 30 seconds; 2 participants

(16.7%) could stand and walk independently. CHOP INTEND scores increased by 9.8 points after 1 month and 15.4 after 3 months in the high-dose group compared with a decrease in untreated SMA type 1.⁶⁴ Furthermore, all 15 patients achieved 20 months of age and did not require permanent ventilation compared with 8% of participants in the historical cohort who were free from permanent ventilation at the time of data collection. There were 56 serious adverse effects (AEs) reported in 13 participants across both cohorts. Two AEs were treatment-related grade 4 elevated serum aminotransferase levels. Another 241 non-serious AEs occurred, with just three being treatment related. Fourteen participants also experienced respiratory illness in the treatment group. Overall results showed that a single onasemnogene intravenous infusion positively affected survival and motor function among infantile-onset SMA.⁶⁴ A subsequent follow-up study is underway assessing long-term safety among 13/15 of the participants who received onasemnogene and will be followed for up to 15 years.⁶⁵

Another study comparing untreated patients with SMA type 1 in the NeuroNEXT (NCT10736553) trial had a 100% survival rate among infants treated with onasemnogene compared with 38% in the NN101 cohort.^{41,66} The baseline mean CHOP INTEND score was 28.2 and improved to 56.5 in the onasemnogene group compared with 20.3 with a decrease to 5.3 in the NN101 group after 24 months. Furthermore, 92% of the onasemnogene patients could sit independently for 5 seconds or more, 83% for 10 seconds or more, 75% for 30 seconds or more, and 17% (2 people) could stand and walk unassisted. In contrast, CHOP INTEND scores in the NN101 cohort did not suggest any motor milestones being achieved.⁶⁶

Results from the STRIVE-US trial (NCT03306277) evaluating the safety and efficacy of onasemnogene used in symptomatic patients with SMA type 1 (aged <6 months with 2 *SMN2* copies) were recently reported.⁶⁷⁻⁶⁹ This phase 3, open-label, single-arm, single-dose, gene replacement trial administered onasemnogene via intravenous infusion and 91% of patients met the co-primary efficacy end point of event-free survival at 14 months and 59% met functional sitting for 30 seconds or longer at 18 months of age ($P < .0001$ vs. natural history).⁶⁹ Also, 68.2% of patients remained free of noninvasive ventilation during the study, and 81.8% were free of ventilation at 18 months of age. Twenty-one patients achieved CHOP INTEND scores greater than or equal to 30, and fourteen achieved a score greater than or equal to 50.⁶⁷ This study also was the first to introduce the “ability to thrive” composite measure defined as the proportion of infants able to maintain a healthy body weight without nutritional support. Of the 22 participants, 40.9% ($P < .0001$ vs natural history) demonstrated the ability to thrive at 18 months of age, with 19 participants not requiring a feeding tube, 14 maintaining a good weight, and 12 able to tolerate thin liquids.⁶⁹ There was 1 AE reported in all 22 participants (12 that were deemed treatment related). The most commonly reported AEs

were pyrexia, upper respiratory tract infections, constipation, and scoliosis, considered manageable and consistent with the drug safety profile.⁶⁷⁻⁶⁹

Another phase 3 trial, SPRINT (NCT03505099), is an open-label, single-arm trial evaluating the safety and efficacy of onasemnogene pre-symptomatically in infants with SMA younger than 6 weeks old with 2 or 3 copies of *SMN2* (similar to the NURTURE trial).⁷⁰ Interim data analysis with a December 31, 2019 cutoff was conducted to determine preliminary results. Results of these data showed that 57% (8/14) of participants with 2 copies of the *SMN2* gene could sit independently for at least 30 seconds, and 28.5% (4/14) could walk independently.⁶⁹ All participants with 2 *SMN2* copies achieved or maintained CHOP INTEND scores greater than or equal to 50 (with 13 \geq 58). Among SMA type 1 natural history patients, individuals rarely score 40 or above on CHOP INTEND. Also, 26.5% (4/15) of participants with 3 copies of the *SMN2* gene could stand independently for at least 3 seconds, and 20% (3/15) could walk independently. AEs were reported after administration in all participants with 17 deemed treatment related.⁶⁹ The most common AEs were pyrexia, upper respiratory tract infection, constipation, and nasopharyngitis. Six patients had serious AEs, but they were not deemed to be treatment related.⁶⁹ For this 2019 analysis, many of the patients who had not yet achieved certain motor milestones were still within the appropriate age range for continued development.⁶² As the data continue to be collected, the results from the study may become more robust.⁶²

START Long-Term Follow-Up (START LTFU) is an ongoing observational, long-term follow-up study from the patients who completed the phase 1 START trial and received onasemnogene.⁶⁹ As of December 31, 2019, ten of the 12 participants from the second cohort of START who enrolled in the LTFU study were alive and did not require permanent ventilation. Also, there were no previously achieved motor milestones lost during the follow-up period. Two patients achieved a new milestone of standing with assistance (and did not receive treatment with nusinersen during the follow-up period). None of the patients who were free from ventilation at the end of START have had to initiate new ventilation support during the follow-up period. Also, 60% (6/10) of participants also do not require daily respiratory support after more than 4 years from receiving their onasemnogene dose. No new treatment-related severe adverse events or AEs of note occurred during the long-term follow-up study.⁶⁹

Onasemnogene has also been studied for intrathecal administration.^{71,72} The phase 1/phase 2 trial STRONG investigated the safety of 2 different doses of onasemnogene when given via the intrathecal route. A total of 32 patients were enrolled in the study. Two groups were created, those older and younger than 2 years. Participants' ages ranged from 6 months to 5 years. The STRONG trial has been on hold since October 2019. In preclinical data, there

was inflammation found in primates secondary to the intrathecal administration of onasemnogene. Although this has not been seen in any of the human participants, the FDA is conducting a full investigation of the preclinical findings.^{71,72}

Overall cumulative safety data from all trials and postmarketing surveillance suggest that patients experience AEs from onasemnogene, but they are generally manageable and not serious.⁶⁹ One potentially serious AE is liver injury.⁷³ Liver transaminase elevations need to be monitored via liver function tests and should be managed with prophylactic prednisolone started 1 day before treatment and continued for at least 30 days.⁷³ Liver injury and hepatotoxicity can be serious without appropriate monitoring and intervention.⁷⁴ Feldman and colleagues reported 2 cases of transient drug-induced liver failure with use of onasemnogene. Teams considering use of onasemnogene in their practice may want to consider inclusion of a hepatologist in the patient care team. Thrombocytopenia has also occurred but usually is transient and resolves without intervention and monitored via platelet counts. Postmarketing surveillance has also noted reports of heart rate changes and laboratory anomalies that are not explained clinically. Therefore, troponin I should also be monitored in patients receiving onasemnogene. No dorsal root ganglia inflammation has been observed clinically at this time. No new deaths have been reported in either the STRIVE-US or STRIVE-EU trials; the 2 reported deaths were determined to be unrelated to drug therapy based on autopsy findings.⁶⁹

Risdiplam

Risdiplam is the first oral, small-molecule, SMN2 splicing modifier that increases functional SMN protein.⁷⁵ Risdiplam is approved in patients aged 2 months and older and is available as an oral liquid that can be administered by mouth or via feeding tube.⁷⁶ Dosing is both weight and age based for risdiplam. Patients between 2 months and 2 years of age will receive 0.2 mg/kg of their body weight of risdiplam regardless of weight. For patients 2 years and older, dosing is 0.25 mg/kg body weight with a maximum dose of 5 mg recommended in all patients 20 kg and greater.⁷⁶ Risdiplam is dispensed in amber, glass bottles for protection from light and pharmacists will need to dispense the appropriate amber syringes for the patient's dose. Risdiplam is manufactured as a 0.75-mg/mL oral solution. It was FDA approved in August 2020 to treat SMA in patients aged 2 months and older.⁷⁷ Approval of this agent was based on 2 pivotal trials: FIREFISH and SUNFISH.

FIREFISH (NCT02913482) was an open-label, 2-part phase 2/3 trial in infants with SMA type 1 aged 1 to 7 months.⁷⁸ Part 1 (N = 21) included a dose-finding study and a safety evaluation. Part 2 (N = 41) evaluated the efficacy of risdiplam. The primary efficacy objective was measured using the proportion of infants sitting without support for 12 months of treatment and longer using the Gross Motor Scale of the BSID-III.⁷⁸ Part 1 results showed that key motor

milestones were met after 1 year of treatment with risdiplam.⁷⁹ Of the 17 participants who received the part 2 study dose, 41.2% (7/21) were able to sit independently for a minimum of 5 seconds. Also, 64.7% (11/17) could sit with or without support, and 52.9% (9/17) achieved upright head control after 12 months of treatment measured via the HINE-2. One infant was also able to stand by 12 months. Part 1 also used CHOP INTEND to assess motor function. Of the 17 participants, 58.8% in the risdiplam group achieved a CHOP INTEND score of 40 or more points. The CHOP INTEND median change from baseline to month 12 was 17.5 points. Among all 21 participants, none of the infants lost the ability to swallow, required tracheostomy, or permanent ventilation. The most common AEs were pyrexia, upper respiratory tract infections, diarrhea, vomiting, cough, pneumonia, and constipation.⁷⁹ Preliminary final results of part 2 were recently presented and showed event-free survival time was vastly improved among those treated with risdiplam compared with natural history SMA.⁸⁰ The majority of infants also retained their ability to swallow and feed. Almost half of the risdiplam-treated patients did not require hospitalization up to 12 months.⁸⁰

SUNFISH (NCT02908685) is a second phase 2/3, randomized, double-blind, placebo-controlled extension study evaluating the safety, tolerability, and effectiveness of risdiplam in SMA types 2 and 3 in individuals aged 2 to 25 years who are not ambulatory.⁸¹ Part 1 (N = 51) examined the safety, pharmacodynamics, pharmacokinetics, and optimal dose of risdiplam. Part 1 showed treatment with risdiplam resulted in a median 2-fold increase in blood SMN protein levels after 4 weeks, which were sustained for a minimum of 24 months.⁸² Motor function measure (MFM) total change from baseline at month 24 was also larger in patients treated with risdiplam (3.99-point difference, 95% CI, 2.34-5.65; $P < .0001$). Part 2 of the SUNFISH trial results were recently presented. A change in baseline of the MFM-32 scale was significantly greater in risdiplam-treated patients compared with placebo (-1.55-point mean difference; $P = .0156$). The greatest response in MFM-32 was observed in the 2- to 5-year age group versus placebo and disease stabilization in the 18- to 25-year age group. The safety profile was consistent with other risdiplam trials, and the most common AEs were upper respiratory tract infections, nasopharyngitis, pyrexia, headache, diarrhea, vomiting, and cough.⁸¹

JEWELFISH (NCT03032172) is a phase 2, open-label exploratory trial in patients with SMA types 1 to 3 between the ages of 6 months and 60 years who have also received previous treatment for SMA with nusinersen, onasemnogene, or olesoxime.^{82,83} The study enrolled 174 participants with 76 previously treated with nusinersen and 14 with onasemnogene. The other 83 participants had been treated with other compounds under development by the manufacturer. The most common AEs observed were upper respiratory tract infections, headache, fever, diarrhea, nasopharyngitis,

and nausea. No drug-related safety findings have led to withdrawal from JEWELFISH to date, and AE profiles are consistent with those found in risdiplam trials with SMA-targeting therapy-naïve patients.⁸² This study is ongoing and has an estimated study completion date of January 31, 2025.

RAINBOWFISH (NCT03779334) is an open-label, single-arm, multicenter study that is ongoing and evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants from birth to 6 weeks old genetically diagnosed with SMA and pre-symptomatic.⁸⁴ RAINBOWFISH is currently recruiting and is expected to enroll 25 participants. Each participant will be given oral risdiplam once daily for 2 years and then enrolled in an open-label extension and follow-up. The estimated completion date is July 22, 2026.⁸⁴

Conclusions

In summary, SMA is an inherited neuromuscular disorder that results in a wide variety of clinical burdens. Disease severity correlates, although imperfectly, with *SMN2* copy number. Before 2016, there were no disease-modifying therapies, and patients and caregivers relied on supportive care. The natural history of SMA has evolved over the years as additional research and technologies have improved our understanding of the pathologic mechanisms responsible for SMA. Increased understanding has also resulted in the development of novel disease-modifying therapies that have led to patients achieving motor milestones and survival outcomes never before possible. There are now 3 disease-modifying therapies FDA approved and commercially available for use in patients with SMA. Therefore, it is crucial that pharmacists, as integral members of the SMA care team, have a thorough understanding of efficacy and safety data for these agents to improve clinical decision making and outcomes among affected patients with SMA. ■

Author affiliation: Dr Bisaccia is a clinical pharmacy specialist at Rush University Medical Center in Chicago, IL.

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Address correspondence to: elizabeth_k_bisaccia@rush.edu

Medical writing and editorial support provided by: Brittany Hoffmann-Eubanks, PharmD, MBA.

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Spinal Muscular Atrophy: An Update for Managed Care Pharmacists

Alan D. Pannier, PharmD, MBA

Importance of Early and Effective Treatment in Spinal Muscular Atrophy

Cost of Care

The cost burden of patients with spinal muscular atrophy (SMA) is significant and varies due to the type of SMA and medications used. In a study conducted from January 2006 to March 2016 (before approval of pharmacologic therapy), investigators evaluated healthcare resource utilization and costs in patients. A total of 341 patients with SMA included in the analysis were stratified by infantile-onset SMA before age of 6 months (mean age, 0.2 years; n = 22), childhood-onset SMA between 6 months and 3 years of age (mean age, 0.9 years; n = 22), and late-onset SMA, which included all other patients with SMA (mean age, 52.2 years; n = 296), then were compared with a cohort without SMA. Medications that these patients used during their follow-up period were consistent with physical symptoms of SMA, such as gastroesophageal reflux disease, respiratory tract infections, muscle spasm, difficulty moving muscles and joints, and concurrent mental health disorders. Medications that have been used most commonly were acid suppressants, antibiotics, muscle relaxants, benzodiazepines, prokinetic agents, and anxiolytics. Of note, those with infantile SMA have observed higher rates of acid suppressants and prokinetic agents, whereas those of older-onset SMA had more use of muscle relaxants, benzodiazepines, anxiolytics, and antidepressants. Although these medications are generically available and inexpensive, there is an increased burden of higher medication usage. These medications are summarized in [Table 1](#).¹

Along with increased medication usage, there was a significant number of patients with SMA who required utilization of costly resources. More patients with infantile SMA used a mechanically assisted cough device compared with late-onset SMA (52.2% vs 1.2%). Other healthcare resources that were highly utilized in infantile SMA included noninvasive ventilation (26.1%), invasive ventilation (17.4%), and gastrostomy tube (34.8%). A summary of common healthcare resources utilized from this study is shown in [Table 1](#).¹

The high rates of medication usage and healthcare resource utilization translate into high costs associated with SMA. On a

ABSTRACT

The cost burden of patients with SMA is considerable, and is estimated to be approximately \$4 million to \$5 million over 10 years in patients with early-onset SMA. This cost is 54.2 times greater than an otherwise healthy population. The utilization of medication, resources, and cost differs between different types of SMA and is more intensive in infantile-onset SMA type 1. Patients often require supportive physical aides, ventilation, and other services to treat sequelae of muscle weakness. Early diagnosis and treatment initiation are necessary to maximize benefit of treatment. Genetic newborn screening has allowed for early diagnosis. With the approval of novel pharmacotherapy options for SMA, timely treatment initiation may help to decrease healthcare burden and costs associated with early-onset SMA. Current options are effective in improving mobility, but maximum benefit has yet to be seen as this population is still growing. Due to the cost of treatment, managed care pharmacists should consider appropriate utilization management and innovative outcomes-based payment models to decrease risk while maximizing outcomes.

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per-member per-month (PMPM) basis, those in the infantile SMA group had the highest mean costs (\$25,517) followed by childhood onset (\$6357) and late onset (\$2499). In the matched cohort without SMA, the cost was significantly lower in the infantile group (\$406), childhood onset (\$188), and late onset (\$742). A comparison of these costs is outlined in [Table 2](#).¹ It is also important to note that the average cost to treat a patient with infantile-onset SMA was 54.2 times higher than someone without SMA during a similar

follow-up period; childhood onset was 33.7 times higher; and adult onset was 3.1 times higher.¹

In a separate Institute for Clinical and Economic Review (ICER) evaluation of nusinersen and onasemnogene abeparvovec-xioi for SMA, evaluators estimated the annual cost of best supportive care (BSC) for SMA to be approximately \$167,400 excluding any FDA-approved pharmacologic therapy. This is similar to other estimates of cost of care associated with routine SMA care.² In a 2010

evaluation of total annual costs, those with early-onset SMA (<3 years old) had an estimated cost of \$184,647 per patient compared with other SMA at \$45,750 a year. Of the costs associated with early-onset SMA, \$115,223 were directly attributable to medical costs. Total nonmedical costs were estimated to be \$51,655 for this early-onset SMA population. When broken down by individual costs, professional caregiving made up a majority of annual costs (\$50,542), followed by moving/home modification (\$3685), other nonmedical costs such as food and travel (\$2106), and purchasing/modifying transportation (\$1814).³ It should be noted that these cost estimates were prior to FDA-approved pharmacotherapy options for SMA. Cost estimates were higher for SMA type 1 due to extensive healthcare needs and disease severity compared with later-onset SMA. This high healthcare burden on patients with early-onset SMA underlies the essential need for effective and early management of symptoms, which may have the potential to decrease costs associated with these symptoms.

Disease Progression and Need for Timely Diagnosis and Treatment

Left untreated, SMA results in significant comorbidities and mortality. Depending on the type of SMA (type 0-4), age of onset and clinical presentation will vary. In those with untreated SMA type 1, patients may never sit/stand and death will likely occur within the first 2 years of life. These patients suffer from physical symptoms of reduced muscle tone, decreased limited movements, difficulty with eating and swallowing, and impaired breathing that can lead to respiratory depression. In patients with SMA type 2, life expectancy is longer (young adult) than type 1 but also results in the need for mobility aids as well as potential need for

TABLE 1. Common Medications and Healthcare Resources Identified in an SMA Population¹

	Infantile SMA (n = 23)	Childhood-onset SMA (n = 22)	Late-onset SMA (n = 296)
Mean length of follow-up	11 months	27.7 months	36 months
Common Medications			
Acid suppressants	56.5%	31.8%	28.7%
Antibiotics	56.5%	68.2%	67.2%
Muscle relaxants	17.4%	31.8%	36.8%
Benzodiazepines	17.4%	31.8%	36.1%
Prokinetic agents	13.0%	4.5%	3.4%
Anxiolytics	8.7%	9.1%	21.3%
Antidepressants	0%	0%	31.8%
Botulinum toxin	0%	0%	2.4%
CNS stimulants	0%	0%	6.4%
Healthcare Resources			
Mechanically assisted cough devices	52.2%	31.8%	1.4%
Noninvasive ventilation	26.1%	9.1%	4.1%
Invasive ventilation	17.4%	13.6%	1.0%
Enteral feeding products	60.9%	39.4%	5.1%
Gastrostomy tube	34.8%	13.6%	2.0%
Orthotics	30.4%	54.5%	27.0%
Orthopedic surgery	17.4%	22.7%	38.5%
Durable medical equipment	13.0%	45.5%	14.5%
Scoliosis correction surgery	4.3%	4.5%	2.0%

CNS, central nervous system; SMA, spinal muscular atrophy.

TABLE 2. Mean Costs of Treating Patients With SMA Compared With a Cohort Without SMA¹

	With SMA (PMPM)	Without SMA (PMPM)	Average higher cost in SMA vs without SMA (95% CI)
Infantile onset	\$25,517	\$406	54.2 times higher (27.2-107.9)
Childhood onset	\$6357	\$188	33.7 times higher (15.9-71.6)
Adult onset	\$2499	\$742	3.1 times higher (2.5-3.8)

PMPM, per-member per-month; SMA, spinal muscular atrophy.

ventilation. Those with type 3 have the potential to live a typical lifespan with treatment but have an increased risk of respiratory infections and musculoskeletal concerns, such as scoliosis and muscle/joint weakness. Those with SMA type 4 usually have mild-moderate physical symptoms and a normal lifespan.⁴ Historically, there has been a delay in SMA diagnosis of 3.6, 14.3, and 43.6 months for SMA types 1, 2, and 3, respectively.⁵ This delay in diagnosis may lead to irreversible disease progression and worsening prognosis. It is thought the delay occurs due to symptoms varying widely in onset and severity and can resemble other diseases. Additionally, the lack of expertise in the field can lead to healthcare professionals ruling out other diagnoses before considering SMA.

To mitigate these detrimental effects and high mortality rate, early diagnosis and appropriate treatment are essential. Genetic testing for SMA due to homozygous deletion of exon 7 in SMN1 has been added to the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of disorders that the Secretary of the Department of Health and Human Services recommends adding to each state's universal newborn screening (NBS) program. Disorders are added to the list if there is (1) a net benefit for screening, (2) the ability to screen for the disorder, and (3) the availability of effective treatments. Non-grandfathered health plans are also required to cover screenings for conditions listed on the RUSP without a co-payment, co-insurance, or deductible.⁶ As of 2020, 28 states had incorporated SMA into routine NBS, and 5 states have implemented SMA NBS pilot programs as a result of the RUSP guidelines.⁷

If newborns are positively screened for SMA types 0-3, patients should receive immediate treatment if pre-symptomatic. In those with SMA type 0, physician discretion should be used if the patient presents with symptoms. The effective treatment of patients before symptom manifestation may help to maintain motor neurons and preserve muscle motor function.^{8,9} This efficacy was demonstrated in clinical trials, but the true lifelong benefit of treatment has yet to be seen because the first pharmacotherapy option was approved in 2016. Recent releases of long-term safety and efficacy checkpoints do show continued durability of treatments. In clinical trials, all currently approved FDA therapies for SMA observed more benefit in patients treated earlier in their disease pathway.¹⁰ Current pharmacotherapy is approved in pediatrics and adult patients, but clinical trials have not included those with SMA type 4 (older onset). Before the approval of these therapies, disease management consisted

of symptomatic management (eg, muscle relaxants, antibiotics), mobility aides (eg, walker, wheelchair), and other therapies. It is important to have open communication and coordination among the managed care organization and provider support staff to ensure timely treatment. Newborns have up to 30 days to be added to insurance benefits of parents and coverage will be backdated to the newborn day of birth. Additionally, under the Health Insurance Portability and Accountability Act, if enrolled within 30 days of birth, insurance companies may not impose preexisting condition exclusions on the newborn.¹¹

Costs Associated With Treatment of SMA

In 1 claim-based healthcare resource utilization review of patients with SMA from September 1, 2016 to August 31, 2018, patients were categorized into 4 cohorts: (1) patients with SMA type 1, (2) patients with SMA type 1 on nusinersen, (3) patients with other types of SMA, and (4) patients with other types of SMA on nusinersen. When the cost of nusinersen was excluded, the annual cost of treating patients with SMA type 1 (no nusinersen) was \$137,627 compared with \$92,618 in the SMA type 1 on nusinersen group. This may have been associated with a decrease in annual inpatient days of 14.1 and 4.6, respectively. However, this decrease in medical visits per year and annual cost without nusinersen was not consistent with other types of SMA. Authors noted limitations to their results, which included potentially underestimated costs that were not in the claims system. While limited, these data support that for those with SMA type 1, treatment of nusinersen reduced healthcare resource utilization and other total costs. These cost savings were offset by the real-world cost of nusinersen, which was \$191,909 PMPM for the first 3 months (loading dose) followed by \$36,882 PMPM for maintenance costs. The study results are summarized in [Table 3](#).¹²

In an ICER review of nusinersen and onasemnogene abeparovect-xioi for SMA, costs per quality-adjusted life-year (QALY) gained were described by type of SMA and intervention. For SMA type 1, the total cost of treatment with nusinersen and nontreatment healthcare costs were \$3,884,000 compared with \$789,000 for BSC. Nusinersen use was associated with total QALY gained of 3.24 years, total life-year (LY) gained of 7.64 years, and cost/QALY of \$1,112,000. This is in comparison with onasemnogene abeparovect-xioi, which had a relatively similar total cost of care of \$3,657,000, a total of 12.23 QALY gained, 18.17 LY gained, and a cost/QALY gained

TABLE 3. Summary of Results of a Claim-Based Healthcare Resource Utilization Review¹²

	SMA type 1 (n = 349)	SMA type 1 + nusinersen (n = 45)	Other types of SMA (n = 5728)	Other types of SMA + nusinersen (n = 404)
Average medical visits per year	59.4 days	56.6 days	44.5 days	63.7 days
Annual cost without nusinersen	\$137,627	\$92,618	\$49,175	\$76,371

SMA, spinal muscular atrophy.

of \$243,000. It should be noted that this was before the approval of risdiplam, the other medication approved for the treatment of SMA. These results are summarized in **Table 4**.^{2,13}

Researchers from this ICER analysis concluded that neither nusinersen nor onasemnogene abeparvovec-xioi met \$150,000 per QALY gained to meet traditional cost-effectiveness thresholds. Nusinersen was the most cost-effective in the pre-symptomatic population, but the cost would still need to be reduced to \$65,000 a year for it to meet traditional cost-effectiveness.² When interpreting the cost-effectiveness of ultra-rare disorders, it is important to consider that traditional thresholds of cost per QALY gained may need to be reconsidered. With these novel treatments for ultra-rare disorders, higher costs for QALY gained may become more common.

In a separate study, authors examined the cost-effectiveness of onasemnogene abeparvovec-xioi and nusinersen. This study found an LY gain of 37.20 for onasemnogene abeparvovec-xioi and 9.68 LY for nusinersen. This was considerably higher than the ICER estimations of 18.17 LY for onasemnogene abeparvovec-xioi and 7.64 LY for nusinersen.¹⁴ It should be noted that, due to the one-time administration, the longer a patient's life, onasemnogene abeparvovec-xioi becomes more cost-effective. Because we have yet to see the full benefit and lifespan of these patients, the full cost-effectiveness of treatment is to be determined. Managed care pharmacists should be aware of ongoing long-term safety and efficacy follow-up studies in patients who were administered onasemnogene abeparvovec-xioi to continuously update their understanding on the cost-benefit of gene therapy compared with more traditional medications. As favorable long-term safety and efficacy data continue to become available, it is expected to have an adjusted impact on the cost-effectiveness of SMA treatments.

Limited data are available regarding the cost-effectiveness of risdiplam for the treatment of SMA. However, treatment strategies should follow the same strategy as other available agents. Early diagnosis and initiation of therapy as soon as possible prevent loss of neurons and muscle function. Potential advantages with risdiplam include an oral formulation that would not need to be administered by a healthcare professional.

Managed Care Considerations for the Management of SMA

At this time, ICER could not identify any opportunities to reduce unnecessary costs for patients with SMA. However, because of high drug costs and uncertain long-term efficacy and safety, managed care organizations (MCOs) should develop appropriate coverage criteria based on the most current clinical evidence as well as guidelines and input from local providers. Of note, a set of recommendations regarding coverage criteria for SMA pharmacotherapy was proposed. The considerations include²:

1. **Diagnosis:** Should be confirmed via genetic testing, without the need for more than one genetic test.
2. **Pre-symptomatic SMA:** Through genetic testing, patients can be screened for number of SMN2 copies where 4 or more copies may predict less severe forms of SMA. Current recommendations support the immediate initiation of pharmacotherapy in patients who test for 4 or fewer copies of SMN2.
3. **Age:** Pre-symptomatic patients should begin therapy immediately. Evidence does not support loss of efficacy in patients with SMA type 2-3 at all ages. Therefore, there should not be an age restriction for use.

TABLE 4. Cost and QALY Gained With Nusinersen and Onasemnogene abeparvovec-xioi for SMA^{2,13}

	Drug treatment cost	Total costs	QALY gained	Cost/QALY gained vs BSC
SMA type 1				
Nusinersen	\$2,231,000	\$3,884,000	3.24	\$1,112,000
Onasemnogene abeparvovec-xioi	\$2,000,000	\$3,657,000	12.23	\$243,000
BSC	--	\$789,000	0.46	--
SMA type 2/3				
Nusinersen	\$7,634,000	\$9,148,000	12.28	\$8,156,000
BSC		\$1,442,000	11.34	--
Pre-symptomatic SMA				
Nusinersen	\$10,565,000	\$11,929,000	21.94	\$709,000
Onasemnogene abeparvovec-xioi ^a	-- ^a	\$3,264,000	6.25	\$157,000
BSC		\$801,000	6.25	--

BSC, best supportive care; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy.

^aThis estimation was hypothetical and used onasemnogene abeparvovec-xioi pricing with QALY and outcomes associated with nusinersen.

Adapted with minimal changes from Tables 5 and 6 from Thokala P, et al. Cost effectiveness of nusinersen for patients with infantile-onset spinal muscular atrophy in US. *Cost Eff Resour Alloc.* 2020;18(1):41, under a Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

4. **Other clinical criteria:** Pre-symptomatic patients should not have any additional requirements. It is debatable if patients who are immobilized or with more severe symptoms should be eligible for treatment. Some MCOs may also place restrictions on patients who are already on permanent ventilation. However, advocates have noted that small motor improvements can result in large quality-of-life gains in patients.
5. **Renewal criteria:** A baseline assessment should be documented using a standard outcome measure. This baseline can serve as a guideline for evaluation of disease stability or improvement. For nusinersen and risdiplam, MCOs may require documentation of treatment success needed for continued approvals. Every patient is unique, and the provider managing the patient should assess if there has been improvement or at least a halt of disease progression to justify continued approvals.
6. **Combination or sequential therapy:** MCOs should monitor for concurrent use of FDA-approved treatments for SMA and closely monitor switching between agents if an inadequate response is seen in one therapy. Implications for switching should be evaluated and considered on a case-by-case basis in the current absence of strong clinical data on the subject.

When developing coverage criteria for medications used for SMA, managed care pharmacists should also take into consideration drug-specific characteristics, such as indication, approved age range, administration concerns, and significant safety concerns. **Table 5** summarizes these considerations.¹⁵⁻¹⁷ Considerations for nusinersen include evaluation for spinal deformities, planning for regular intrathecal administration, and coordination with the patient to ensure access to a location for appropriate administration. Costs of these administrations should consider things like transportation and lodging, especially in geographically isolated patients. While risdiplam has fewer administration concerns (oral solution), it lacks long-term safety and efficacy data and is only indicated for patients 2 months and older. Onasemnogene abeparvec-xioi is administered once and is only indicated for patients

who are younger than 2 years and meet eligibility requirements. Patients with late-onset SMA would not fit into this demographic.

Because of the high cost of treatment with onasemnogene abeparvec-xioi, and unknown long-term efficacy, MCOs may consider an outcomes-based payment contract with the manufacturer. By establishing an outcomes-based payment contract, the MCO can transfer some of the financial risk back to the manufacturer if outcomes are insufficient.¹⁸ However, these outcomes should be quantifiable, widely accepted outcomes. With SMA, a challenge for implementing an outcomes-based payment contract will be determining what is an appropriate outcome response, and what constitutes an inadequate response. By tying financial risk or health outcomes, MCOs can hold manufacturers to their efficacy data in a real-world setting.^{2,19}

In an example of this outcomes-based payment contracting, the manufacturer of onasemnogene abeparvec-xioi offers an option to pay over multiple years and engage in outcomes-based payments to bring the overall medical cost to within a more cost-effective range.²⁰ As this payment model is still novel, MCOs should pay extra attention to how payments are made and how outcomes have affected payments overall. Future studies on how this outcomes-based payment model has affected overall cost-effectiveness will help to make future formulary determinations.

Regardless of treatment selection, coverage criteria should consider FDA-approved indication, current efficacy, safety data, and diagnosis based on genetic testing. As evidence continues to develop, managed care pharmacists should strive to incorporate the most updated recommendations into coverage criteria. For example, in a recent update to SMA diagnosis, immediate pharmacotherapy is recommended for infants who screened positive for 4 copies of SMN2 (indicative of SMA type 3 or 4).⁸ Managed care pharmacists should focus on minimizing inappropriate utilization and maximizing treatment potential through encouragement of early diagnosis and treatment.

Once an appropriate treatment has been determined, it is important to have effective coordination between the medical and

TABLE 5. Managed Care Considerations for Pharmacotherapy Treatment Options for SMA¹⁵⁻¹⁷

	Nusinersen	Onasemnogene abeparvec-xioi	Risdiplam
Indication	Treatment of SMA in pediatric and adult populations	Treatment of SMA with bi-allelic mutations in the SMN1 gene	Treatment of SMA
Age range	Newborns and older	Younger than 2 years	2 months and older
Administration	Initially, 4 loading doses; then maintenance intrathecal injections every 4 months	1 intravenous infusion	Once daily oral solution
Warnings and precautions	Thrombocytopenia, coagulation abnormalities, renal toxicity	Acute serious liver injury, thrombocytopenia, elevated troponin-I	Fever, diarrhea, rash

SMA, spinal muscular atrophy.

pharmacy benefit. Current SMA treatments offer a unique challenge in that the 3 current products have the potential for 3 unique methods of coverage and payment. Risdiplam as an oral therapy would be processed and evaluated for medical necessity under the pharmacy benefit that is managed by a pharmacy benefits manager. Nusinersen requires administration by a healthcare professional and would typically be evaluated and covered under the medical benefit managed by a medical payer or third-party administrator. Onasemnogene abeparvovec-xioi as a one-time infusion would be processed under the medical benefit with the required inpatient costs associated with administration. Given the various stakeholders involved, lack of coordination has the potential to result in mixed messaging of approval or denial due to the differences in criteria by the different vendors.

Conclusions

The cost burden of early-onset SMA is significant and can cost approximately \$184,647 per patient per year compared with other types of SMA at \$45,750 a year. The significantly higher costs associated with earlier-onset SMA can be attributed to increased need for extensive physical supportive care and medical needs. Advances in the ability to genetically screen for SMA, as well as the availability of novel treatment options that should be started before symptom development, offer MCOs and providers an opportunity to address patients with SMA like never before. By treating SMA before symptom development, there is a potential to mitigate disease progression and improve patient outcomes. Current pharmacotherapy is recommended in patients who are pre-symptomatic at all types of SMA. Each treatment option has a different route of administration, method of payment, and potential advantages. Regarding cost-effectiveness, it was estimated that onasemnogene abeparvovec-xioi has a more favorable cost per QALY gained compared with nusinersen in pre-symptomatic type 1 SMA, but neither were determined to be cost-effective when compared with the \$150,000 per QALY-gained threshold. This benefit is augmented with increased lifespan in patients. Managed care pharmacists should take into consideration long-term safety and efficacy data as they are published. Utilization management of these medications should be in accordance with current guidelines and best available evidence. An outcomes-based payment contract should be considered for onasemnogene abeparvovec-xioi to decrease financial risk and aim for optimal health outcomes. ■

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Address correspondence to: alanpannier@gmail.com

Medical writing and editorial support provided by: Andrew Abe, PharmD.

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Sample of Online Posttest

Choose the best answer for each of the following:

- Evidence suggests more than _____ percent of motor units are lost within the first 6 months of age in patients with spinal muscular atrophy (SMA) type 1.**
 - 30
 - 50
 - 70
 - 90
- In 2019, the SMA working group reconvened based on updated clinical data and experience in SMA. Based on that meeting, the SMA treatment algorithm was amended with which of the following:**
 - Immediate treatment for infants with 1 *SMN2* copy
 - Immediate treatment for infants with 4 *SMN2* copies
 - Watchful waiting in lieu of immediate treatment for infants with 2 *SMN2* copies
 - Watchful waiting in lieu of immediate treatment for infants with 6 *SMN2* copies
- Nusinersen was the first disease-specific therapy approved for the treatment of SMA in pediatric and adult patients and works by increasing production of which of the following?**
 - AAV9
 - mRNA
 - SMN2*
 - SMN* protein
- Which of the following dosing protocols is being investigated in the DEVOTE trial for nusinersen in a broad range of patients with SMA?**
 - Two loading doses of 40 mg 14 days apart followed by 28 mg every 4 months
 - Two loading doses of 40 mg 14 days apart followed by 28 mg every 6 months
 - Two loading doses of 50 mg 14 days apart followed by 28 mg every 4 months
 - Two loading doses of 50 mg 14 days apart followed by 28 mg every 6 months
- Onasemnogene is FDA approved for the treatment of SMA in pediatric patients with bi-allelic mutations in the *SMN1* gene and what age group?**
 - 1-7 months only
 - 6 months or older
 - 24 months or younger
 - 24 months or older
- Risdiplam was approved for the treatment of SMA in patients aged 2 months and older as the first _____ agent:**
 - Intramuscular
 - Intravenous
 - Oral
 - Subcutaneous
- Which type of SMA has been associated with the highest annual healthcare cost?**
 - SMA type 1
 - SMA type 2
 - SMA type 3
 - SMA type 4

8. Which of the following was not a common healthcare resource associated with early-onset/infantile SMA?
- A. Mechanically assisted cough devices
 - B. Noninvasive/invasive ventilation
 - C. Gastrostomy tube
 - D. Eye surgery
9. What is an appropriate estimate of annual cost of care for a patient with SMA type 1 (without pharmacotherapy)?
- A. \$15,750 per year
 - B. \$45,100 per year
 - C. \$167,400 per year
 - D. \$500,000 per year
10. Which of the following is true regarding the Institute for Clinical and Economic Review evaluation of therapies for the treatment of SMA?
- A. Traditional cost-effectiveness thresholds of cost per quality-adjusted life-year (QALY) gained may need to be reconsidered in ultra-rare disorders such as SMA.
 - B. Risdiplam met the traditional cost-effectiveness threshold of \$150,000 per QALY gained.
 - C. Treatment with onasemnogene abeparvovec reduced healthcare resource utilization in type 2 and type 3 SMA.
 - D. Treatment with nusinersen did not reduce healthcare resource utilization.

SAMPLE POSTTEST

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