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SPINAL MUSCULAR ATROPHY: OPTIMIZING CLINICAL OUTCOMES WITH NOVEL THERAPIES AND ROLE OF PHARMACISTS: A REVIEW

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ABSTRACT

Spinal muscular atrophy (SMA) is the most common fatal inherited disease in infants, with different types of SMA ranging from mild to extremely severe and terminal. For the most SMA types which typically affect since birth but in some cases don't showcase the symptoms till adulthood. The progression may vary with the time of rapid progression and stasis, although the complete mental, physical and social well-being of the disease has been merely understood. The recent approval of novel therapies for the treatment of SMA has transformed the treatment paradigm and has the potential to increase survival in patients with SMA. Early diagnosis and initiation of therapy is imperative, and pharmacists can facilitate incorporation of these agents appropriately into the treatment plan for patients with SMA. Pharmacists must understand the safety and efficacy data, as well as real-world experience associated with early initiation of treatment, to provide patients, caregivers, and other health care providers on the multidisciplinary team with information about the benefits versus risks associated with available therapies. This article will also incorporate information, allowing readers to follow cases of patients with SMA and providing an opportunity to immediately implement the knowledge gained from the article.

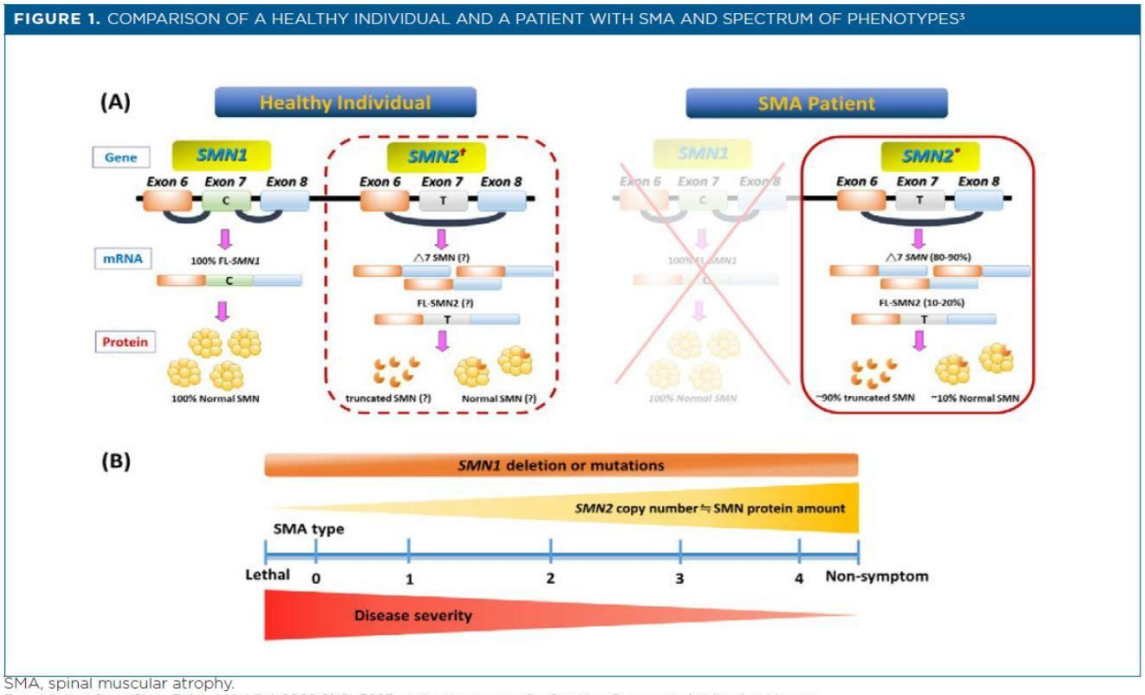
KEYWORDS: Spinal muscular atrophy, Neuromuscular disorder, Motor neurons, Diagnosis, Treatment, Pharmacist.

INTRODUCTION

Spinal muscular atrophy (SMA) is surrounded by a group of disorders with loss of spinal motor neurons. Historically, patients with this disease were managed solely with supportive care to alleviate the associated symptoms and sequelae. However, the recent approval of novel agents to treat this family of disorders has the potential to change the trajectory of the disease process.

Clinical spectrum of SMA

SMA is a progressive, degenerative, inherited neuromuscular disorder. It is an autosomal, recessively inherited group of neuromuscular diseases.[1,2] The genetic basis as well as the phenotype-genotype correlation of SMA is illustrated in **Figure 1**.[3] The main reason of SMA is due to the defects in the survival motor neuron (*SMN*) gene. Most often, the mutation occurs due to a homozygous deletion located on the 5q13 region of the *SMN1* gene, which is responsible for encoding functional SMN1 protein.[4-9] This protein ensures the survival of the α motor neuron. Healthy individuals usually have 2 copies of the *SMN1* gene.[10] The *SMN2* gene is closely related to *SMN1* but differs in its production of protein. Both *SMN1* and *SMN2* play a role in the pathophysiology of SMA. The difference between *SMN1* and *SMN2* is a single nucleotide, but *SMN2* produces less functional protein than its *SMN1* counterpart. For that reason, clinical severity of SMA correlates to the number of *SMN2* copies a patient possesses. A larger number of copies of *SMN2* is associated with less severe manifestation of the disease (**Table 1**).[1,11]



SMA, spinal muscular atrophy.
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Table 1: Clinical presentation of spinal muscular atrophy.

Type	SMN2 Copy Number	Symptoms
1	Most commonly 2, may be 1 or 3	Unable to sit, often have feeding orthopedic and respiratory complications.
2	Most commonly 3, may be 2 or 4	Able to sit, unable to walk, often have feeding, orthopedic and respiratory complication.
3	Most commonly 3 or 4	Able to sit, stand and walk; might have feeding, orthopedic and respiratory complication.
4	Most commonly 4	Mild presentation of symptoms as adult patients.

The characteristic feature of SMA is the degeneration of large motor neurons in the spinal cord and brainstem. The result of this degeneration is a loss of motor function for the patient. SMA is the leading cause of death from genetic disease in infants because patients with the most severe disease will ultimately develop respiratory failure. SMA does not cause neurocognitive degeneration.[12,13] Within the diagnosis of SMA are multiple subcategories with variable levels of severity.[1] Patients diagnosed with SMA type 1 will exhibit the most severe manifestations of the disease. These patients are typically symptomatic by 6 months of age and present with severe hypotonia, including the inability to sit and lack of head control. Historically, patients diagnosed with this category of disease would die by 2 years of age from respiratory failure, unless they were provided mechanical ventilation support. Patients with SMA type 2 present with less severe disease. Symptoms in this patient group typically manifest between 6 and 18 months of age. Though these patients will never be able to walk independently, they will be able to sit independently. Patients with SMA type 2 will continue to develop a progressive weakness and will ultimately be unable to move their arms and legs against resistance. Symptoms in patients with type 3 disease are even less severe, and patients will be able to both walk and sit. However, as the disease progresses in patients with SMA type 3, they may not retain their ability to walk. Onset of symptoms in patients diagnosed with SMA type 3 typically does not occur until the patient is older than 18 months. Patients with SMA type 4 will be diagnosed in adulthood and will exhibit the least severe form of the disease. Patients with SMA type 3 or 4 rarely require mechanical ventilation during their lifetimes.[12,13] SMA affects approximately 10,000 to 25,000 children and adults in the United States.[12,14] The estimated incidence of SMA is 1 per every 6000 to 11,000 live births. The

estimated prevalence of SMA is 1 to 2 per 100,000 people.[12,13,15,16] Because SMA is an autosomal recessive disorder most carriers do not realize they are carriers until they have a child affected by the disease. Carrier frequency is estimated to be 1 in every 25 to 50 people.[17,18] Historically, SMA was diagnosed upon the onset of symptoms.[19] Patients would typically present with proximal muscle weakness, motor delays, or regression in milestones. In current practice, there has been a shift to emphasize the importance of genetic screening and earlier diagnosis. Diagnosis is confirmed with a series of genetic tests, including multiplex ligation-dependent probe amplification, quantitative polymerase chain reaction, and next-generation sequencing. If these tests confirm that a patient is lacking both functional copies of *SMN1*, a diagnosis of SMA can be made. If a patient is found to have only 1 functional copy of *SMN1*, additional testing will be conducted. In rare instances, patients may exhibit symptoms consistent with SMA but will possess 2 functional copies of the *SMN1* gene. Clinicians should then conduct further testing to ensure the patient does not have a rare form of SMA or an alternative neuromuscular disease.[19] When diagnosis was dependent upon the presentation of symptoms, it was commonly delayed for patients to receive their formal diagnosis of SMA.[20-22] The delay could take approximately 4 to 10 months in some patients. In the least severe patients, it could be years before a diagnosis was formalized. With the advent of disease-modifying therapy (DMT) for SMA, the importance of early diagnosis has been emphasized. Patients who have a delayed diagnosis of SMA will not see the same benefit from DMTs. Once α motor neurons degenerate, function cannot be regained because the damage is irreversible. For a patient diagnosed with SMA type 1, 90% of motor neurons will be lost by 6 months of age.[20] In order to expedite the diagnosis of SMA; a new focus has emerged on testing for prenatal carriers and conducting newborn genetic screening. The goal of these new screening methods is to detect SMA earlier and initiate DMT as soon as possible in qualifying patients. SMA was added to the US Federal Recommended Uniform Screening Panel (RUSP) in 2018. At this time, 36 states have adopted and implemented this recommendation with 2 additional states currently progressing towards inclusion of SMA in their state's newborn screening.[20-24]

Caring for Patients With SMA

Traditionally, supportive care with a multidisciplinary emphasis was considered the gold standard for management of patients with SMA. This is outlined in the 2018 SMA Standards of Care. Specialists across a wide variety of disciplines, including but not limited to neurology, orthopaedic, respiratory therapy, pulmonologist, nutrition, pharmacy, and physical therapy,

must be part of the patient care team. Many times, patients will have a care coordinator who works alongside family members to organize services and optimize care.[19,25] Respiratory therapy is a critical component of care for these patients. With the progression of respiratory failure, many patients will require mechanical ventilation during their lifetime. Most patients will require airway clearance with manual chest physiotherapy and mechanical insufflation-exsufflation in order to manage respiratory illnesses, and it must be started proactively.[19,25] Nutrition services and support are also very important as many patients will progress to needing nutrition support through a feeding tube throughout their lifetime. There is also a need for expertise in enteral nutrition products, including elemental formulas and probiotics. Multimodal bowel regimens may often be required as the autonomic nervous system degenerates.[26] Orthopaedic specialists are needed to manage progressive spinal deformities that occur secondary to the neuromuscular disease. They can provide interventions ranging from the creation of braces for the correction of spinal curvature to surgical intervention to correct deformities.[19]

Assessment Scales for SMA

One important aspect of caring for patients with SMA has been quantifying and objectively measuring patients' motor function. Numerous scales have been validated for use and have also been important with the development of novel DMTs as they play a crucial role in qualifying outcomes in the clinical trials. The tests outlined have all been utilized in the clinical trials for DMTs in SMA.[27] The scales are summarized in **Table 2**.[27,28]

Table 2: Spinal muscular atrophy.

Scale	Length	Key considerations
Bayley Scales of Infant Development Third Edition (BSID-III)	45-120 minutes	Assessment of infants and toddlers aged between 1-42 months Multiple sections including behaviour, language and fine motor and gross motor development When assessing motor function, patients will be asked to complete tasks, such as grasping, stacking blocks and sitting Items are scored as able or unable Currently, there are no data to support the use of the BSID-III specifically in the spinal muscular atrophy (SMA) population

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	15-40 minutes	16-item scale developed for patients with SMA type 1 Items scored from 0 (no response) to 4 (complete response) Measures both deliberate muscular movements and reflexive movements Infants with SMA type 1 typically score approximately a 20, whereas those with normal development will often score 40 or above
Hammersmith Functional Motor Scale-Expanded (HFMSF)	10-30 minutes	Evaluate older children (>24 months) with SMA type 2 and 333 items scored from 0 to 2 Assessment is of motor function and expansion of the exam with the items from the Gross Motor Function Measure allows for utilization in both ambulatory and non-ambulatory patients
Hammersmith Infant Neurological Examination Section 2 Motor Milestones (HINF-2)	5-15 minutes	Assess infant motor skills and can be utilized for patients with SMA aged between2-24 months Assesses cranial nerves, motor milestones, posture, tone, reflexes, reactions and behavior Not developed specifically to assess patients with SMA, but has been validated in this patient population and utilized in clinical trials
Motor Function Measure-32 (MFM- 32)	30-50 minutes	32 tasks, patients are scored on a 4 point scale (0 meaning cannot initiate the task and 3 meaning they can complete the task fully) Motor function is examined in 3 different dimensions in this test: axial and proximal motor function, distal motor function, as well as standing and transfers. Patients younger than 7 years may struggle with the length and complexity of this test
Revised Upper Limb Module (RULM)	10-15 minutes	Evaluates upper limb function among primarily nonambulatory children Both upper limbs are evaluated on a 19-item test geared towards assessing activities of daily living Each item scored on a scale of 0 to 2 (with one item being scored as can or cannot) Items include pressing a button, picking up a token and other aspects of everyday life

DMT and Treatment for SMA

In 2018, a treatment algorithm that was created by 15 experts in the field of SMA and moderated by a neutral third party was published to provide guidance in the management of patients with SMA.[20] Their algorithm was meant to provide direction to providers once patients received a positive newborn screen. The authors determined that because patients with SMA have a wide variety of severity, range in acuity, and variable time to onset of symptoms, guidance should be provided on time to treatment. The group created guidance for treatment initiation based on *SMN2* copy number. Infants with 2 or 3 copies of *SMN2* should

be provided immediate treatment. Patients with 1 copy of *SMN2* should receive treatment if pre- symptomatic; when symptomatic, it is left to the physicians' discretion. Patients with 4 or more copies of *SMN2* should be watched closely, and treatment should begin once symptoms present. It was recommended for patients to be evaluated every 3 to 6 months and for parents to keep a watchful eye for any noticeable changes in their child, such as changes to movement, feeding, breathing, or cry. In 2019, this treatment algorithm was updated secondary to newly available data. Per the expert panel, there are now enough data to recommend treating patients including those with 4 copies of *SMN2* from the time of positive newborn screen. The panel continued to recommend waiting and closely monitoring those patients with 5 copies of *SMN2*.[29]

DMTs for SMA are a novel therapeutic area. Studies are ongoing and data are evolving with new interim analyses and regular updates. As such, different sources and reference information may exhibit slight discrepancies depending on date of publication. This article has worked to include the most accurate and up-to-date information available.

Nusinersen

Nusinersen was the first available therapy specific to SMA. Nusinersen is an antisense oligonucleotide that works by causing pre-messenger RNA (mRNA) splicing of the *SMN2* gene in order to increase exon 7 inclusions in *SMN2* mRNA transcripts. Ultimately, this leads to an increase in the production of full-length SMN protein. Nusinersen was approved by the US Food and Drug Administration (FDA) in 2016 for adult and paediatric patients with SMA.[30] Nusinersen is administered to patients via intrathecal injection. Each dose of nusinersen is 12 mg/5 mL. Treatment with nusinersen can be broken down into the loading dose regimen and maintenance therapy phases. When treatment is initiated for patients, 3 loading doses will be given every 14 days. This is followed by a fourth and final loading dose 30 days after the third dose. Once the 4-dose loading regimen is completed, patients can begin maintenance therapy with nusinersen and receive 1 injection every 4 months.[30]

Nusinersen clinical trials

The ENDEAR study evaluated the safety and efficacy of intrathecal nusinersen in 121 infants aged 6 months or younger with infant-onset SMA.[31] Investigators looked at event-free survival and motor milestone response, which was measured using HINE-2. An interim analysis in this study showed that patients treated with nusinersen had higher HINE-2 score improvements (41%) than those in the control group (0%) (P <.001). Patients treated with

nusinersen were also found to have a prolonged time to death or need for permanent ventilation when compared with the control group. The most common adverse reactions to nusinersen were found to be lower respiratory infection and constipation.[30] ENDEAR was terminated early because the data showed overwhelming efficacy for nusinersen, and patients were enrolled in the open-label extension study, SHINE.[31,32] An interim analysis of the SHINE study showed improved Hammersmith scores with nusinersen treatment both at day 1 and day 480. For patients treated with nusinersen, HFMSE scores were 26.5 and 26.1 on days 1 and 480, respectively. For those randomized to the sham procedure, scores were 21.5 and 21.2 on days 1 and 480, respectively.[33] The CHERISH trial examined the use of nusinersen in patients with later-onset SMA, defined as symptom onset after 6 months of age. This study included 126 children aged between 2 and 12 years. Investigators used the HFMSE scoring system to quantify patients' neuromuscular function. Interim analysis in the CHERISH trial showed that patients exhibited a 4-point increase in HFMSE score versus 1.9 mean decrease in score for those in the control group. Fever, headache, vomiting, and back pain were all found to be common adverse reactions to nusinersen.[30] Similar to ENDEAR, CHERISH was also terminated early due to overwhelmingly positive results; patients from CHERISH were enrolled in SHINE.[34,35] The SHINE open-label extension trial began in 2015. The estimated completion date for this trial is August 2023.[32] All patients enrolled in SHINE received nusinersen 12 mg intrathecal injections every 4 months. Patients who received nusinersen in CHERISH and ENDEAR exhibited better motor function than those transitioned from placebo utilizing the HFMSE and RULM scores.[36,37] NURTURE is an open-label, interventional study assessing the efficacy, safety, tolerability, and pharmacokinetics of nusinersen in genetically diagnosed pre- symptomatic infants with SMA aged 6 weeks or younger at the time of therapy initiation.[38] As of February 2020, all 25 patients treated with nusinersen in this trial were alive and did not require permanent ventilation.[39] Compared with historical controls, this is significant as patients with SMA type 1 who remain untreated rarely live beyond 2 years of age. The estimated completion date for this trial is February 2025.[40] Study of nusinersen continues with the DEVOTE trial, a phase 2/3, controlled; dose escalating trial.[41] The study will have 4 treatment arms. The first will include patients with later-onset SMA who will be given nusinersen 28 mg on days 1, 15, and 29, followed by maintenance therapy with 28 mg on days 149 and 269. The second arm will be patients with infant- or later-onset SMA who will receive nusinersen 12 mg intrathecally on days 1, 15, 29, and 64, followed by 12-mg maintenance doses on days 183 and 279. The third arm will include patients with infant- or later-onset SMA receiving loading

doses of nusinersen 50 mg intrathecally on days 1 and 15, followed by 28 mg on days 135 and 279. A sham procedure will be administered on days 29, 64, and 183 in this treatment arm. Finally, participants who have been receiving the approved 12-mg dose for at least 1 year prior to study entry will receive a single 50-mg bolus dose intrathecally on day 1 (4 months following their most recent 12-mg dose), followed by maintenance therapy of nusinersen 28 mg on days 121 and 241. The goal of this study is to determine if a higher dose of nusinersen will increase treatment efficacy. Efficacy will be measured utilizing the CHOP INTEND scoring system. This study is estimated to be completed by July 4, 2023.[41] In January 2021, an announcement of the phase 4 RESPOND trial was made regarding treatment of the first patient in the trial. RESPOND will assess the benefit of nusinersen for infants and children treated with onasemnogene abeparvovec who may have unmet clinical needs after treatment. RESPOND will be a 2-year, open-label study including 60 patients up to 3 years of age at the time of first nusinersen dose. It has been reported that up to 40% of patients in the long-term study of onasemnogene abeparvovec have been treated with nusinersen.[42,43] The available DMTs, nusinersen has been available the longest. There are many observational, post marketing, and surveillance studies currently ongoing. Investigators are also continuing to publish based upon their real-world experience with nusinersen. As these data are published, further evidence is growing for treatment of adult patients, and the hypothesis that earlier treatment results in improved outcomes is being validated. One study found that, overall, nusinersen treatment resulted in improved HFMSE scores and that earlier intervention was associated with the best response to therapy.[44] Of note, investigators did not see any improvement in the progression of scoliosis with nusinersen treatment.[44] The effect of nusinersen in patients with all types of SMA was examined in a 12-month observational study.[45] Investigators noted that clinical trial data may not apply to all patients eligible for treatment with nusinersen and cautioned that extrapolating data from infants may set unrealistic expectations for patients with advanced disease. However, investigators found that improvements made on nusinersen, even small, were meaningful for patients and caregivers.[45] Nusinersen is approved for the treatment of SMA in all ages. The clinical trials discussed have outlined much of the data in infants and children. For adult patients, there are some published reports regarding nusinersen use. Published results of an observational cohort study in patients with genetically confirmed SMA aged between 16 and 65 years found that mean Hammersmith scores significantly improved from baseline with nusinersen treatment. Limitations of the observational study included study design and the natural functional decline of SMA.[46] Another study found that nusinersen provided a mild treatment effect in adult

patients with SMA type 3 as noted in the 6-minute walk test, RULM, and peak cough flow results.[47] There are ongoing studies of nusinersen in adult patients with SMA.

Onasemnogene abeparvovec

Onasemnogene abeparvovec is an adeno-associated virus type 9 (AAV9) vector-based *SMN1* gene therapy. Onasemnogene works to replace the *SMN1* gene encoding human SMN protein. This therapy was approved in 2019 for the treatment of paediatric patients younger than 2 years with biallelic mutations in the *SMN1* gene. FDA approval for this medication was determined based on the completed phase 1 and ongoing phase 3 clinical trials conducted in patients with infant-onset SMA.[48] Onasemnogene is an intravenous infusion administered over 60 minutes. Onasemnogene is dosed by body weight, and the recommended regimen is 1.1 x 10^{14} vector genomes/kg.[48]

Onasemnogene abeparvovec clinical trials

START was a phase 1 clinical trial that included 15 infants with SMA type 1, with 2 copies of *SMN2*.[49,50] This was a single-arm, open-label, dose escalating study. The goal of START was to establish the preliminary efficacy and safety of onasemnogene.[51] The primary outcomes were focused on safety and included treatment-related adverse events (trAEs) of grade 3 or higher. Time until death and need for permanent ventilation were secondary outcomes. Due to observation of elevated serum aminotransferase in the first patient in cohort 1, an amendment was made to the protocol to require concomitant prednisolone administration. At 2 years post infusion, all patients in the high-dose cohort were free from permanent ventilation. Of the 12 participants, 9 in the high-dose cohort could sit independently, and 2 could stand and walk independently. CHOP INTEND scores increased by 9.8 points after 1 month and by 15.4 points after 3 months when compared with untreated controls with SMA type 1. Overall, results showed that a single dose of onasemnogene positively affected survival and motor function in patients diagnosed with infant-onset SMA. The trial also found 56 serious adverse effects (AEs) reported in 13 participants across both cohorts, of which 2 were treatment-related grade 4 elevations in serum aminotransferase levels.[51] The NeuroNEXT trial also studied onasemnogene in untreated patients with SMA type 1.[52,53] This trial exhibited a 100% survival rate for infants treated with onasemnogene compared with 38% in the NN101 cohort. Meaningful changes in CHOP INTEND scores were also identified. Patients treated with onasemnogene improved to a score of 56.5 from a baseline score of 28.2. Patients in the NN101 group exhibited decline to 5.3 from a baseline of

20.3. Those treated with onasemnogene also exhibited significant achievement in motor milestones, which was not documented in the NN101 group. The untreated patients in this study were a historical control group.[52,53] STR1VE-US was a phase 3, open-label, single-arm, single-dose trial that assessed the safety and efficacy of onasemnogene in symptomatic patients with SMA type 1. Participants in this trial included those younger than 6 months who had 1 or 2 copies of *SMN2*. The co-primary end point for efficacy was event-free survival at 14 months; 91% of patients met this end point. Additionally, 59% of patients met the end point of functional sitting for 30 seconds or longer at 18 months of age (P <.0001 vs. natural history). Further, 81.8% of patients were free of ventilation at 18 months of age. This study was the first to introduce the concept of ability to thrive at 18 months of age, a composite measure defined as the proportion of infants able to maintain healthy body weight without nutritional support or intervention. In this measure, 40.9% of study participants exhibited an ability to thrive, including 19 participants not requiring a feeding tube, 14 being able to maintain good weight, and 12 able to tolerate thin liquids. The most common AEs noted in the study were pyrexia, upper respiratory infection, constipation, and scoliosis. All were considered manageable and consistent with the medication's safety profile.[54-56] SPR1NT was an open-label, single-arm, phase 3 trial evaluating the efficacy and safety of onasemnogene in pre-symptomatic infants with SMA.[57] Patients enrolled were younger than 6 weeks with 2 or 3 copies of *SMN2*. In 2019, an interim data analysis was conducted on this trial. This analysis showed that 8 of 14 participants with 2 copies of the *SMN2* gene could sit independently for at least 30 seconds. Additionally, 4 of 14 participants could walk independently. All patients with 2 *SMN2* copies achieved or maintained CHOP INTEND scores greater than or equal to 50. Patients in the trial who had not yet achieved motor milestones during this analysis were found to still be within the appropriate age range for continued development.[55,58] 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. As of December 2019, 10 of 12 participants in the active treatment cohort were alive and did not require permanent ventilation. No previously achieved motor milestones were lost during the follow-up period. Two patients were able to achieve new milestones of standing with assistance. No new trAEs were noted during the follow-up study.[55] The STRONG study is a phase 1 clinical trial with the goal of studying onasemnogene administration intrathecally. This trial has been on hold since October 2019 secondary to inflammation found in primates following the intrathecal administration of onasemnogene.[59,60] Overall, the cumulative safety analysis from the trials and post marketing

surveillance suggests that although patients experience AEs with onasemnogene, they are generally not serious.[55,61,62] However, there is the potentially serious AE of liver injury. Liver transaminase elevations need to be monitored via liver function tests and should be managed with prophylactic-prednisolone. Prednisolone dosing is adjusted based on laboratory results. Prednisolone must be initiated 1 day prior to treatment with onasemnogene and should be continued for at least 30 days following therapy. ALT, AST, total bilirubin, and prothrombin time should all be assessed at the end of the 30-day treatment period for prednisolone. If a patient is found to have normal liver function, steroids can then be tapered over the next 28 days. If liver function abnormalities are noted, systemic steroids should be continued at treatment dosing until assessments have normalized and then steroids can be tapered. If liver function does not improve, a hepatologist should be consulted. It may be helpful to include a hepatologist on the patient care team as well.[48] Liver injury and hepatotoxicity can be serious without appropriate monitoring and intervention.[61] One study reported 2 cases of transient drug-induced liver failure following administration of onasemnogene.[62] Thrombocytopenia has also occurred in patients receiving onasemnogene. However, this has been found to be transient and will resolve without intervention. Close monitoring of platelet counts is still recommended. Post marketing surveillance has shown heart rate changes and laboratory abnormalities that cannot be explained clinically. Patients receiving onasemnogene should have troponin I monitored.[48] Other adverse reactions to onasemnogene can include elevated aminotransferases and vomiting.[48] The manufacturer recently released a statement regarding real-world experience with onasemnogene indicating significant clinical benefit following treatment with this medication. The experience now allows clinicians to see that the benefits can be observed more than 5 years post dosing.[63]

Risdiplam

Risdiplam is the first oral agent to treat SMA and was FDA approved in 2020 for the treatment of patients aged 2 months and older. It is a small-molecule, *SMN2* splicing modifier that increases functional SMN protein.[64,65] It is available as an oral liquid (0.75 mg/mL) that can be administered by mouth or via feeding tube. Dosing for this agent is based both on age and weight. Patients aged between 2 months and 2 years will receive risdiplam 0.2 mg/kg body weight. For patients aged 2 years or older, dosing is 0.25 mg/kg body weight, with a maximum dose of 5 mg. Risdiplam is dispensed in amber glass bottles for protection from light. Pharmacists will need to dispense the appropriate oral syringes for patient use alongside the medication.[65]

Risdiplam clinical trials

FIREFISH was an open-label, 2-part, phase 2/3 trial in infants with SMA type 1 aged between 1 and 7 months.[66,67] The primary efficacy end point was the proportion of infants sitting without support for 12 months of treatment and longer using the BSID-III and CHOP INTEND.[66] Results of the trial showed that key motor milestones were met after 1 year of treatment with risdiplam. Published results from the second part of the FIREFISH study showed that with risdiplam therapy 95% of patients were able to retain the ability to swallow and 89% of patients were able to feed orally.[68] The most common AEs noted for risdiplam were upper respiratory tract infection, fever, rash, and pneumonia.[65] SUNFISH is a second phase 2/3, randomized, double-blind, placebo-controlled extension study. The goal is to assess the safety, tolerability, and effectiveness of risdiplam in patients with SMA types 2 or 3 aged between 2 and 25 years.

Patients in this study are nonambulatory. Part 1 of this study showed that treatment with risdiplam resulted in a median 2-fold increase in blood SMN protein levels after 4 weeks. These changes were sustained for a minimum of 24 months. Another finding was significant change in baseline MFM-32 score between risdiplam-treated patients and those who received placebo.[69,70] The greatest response was noted in patients aged between 2 and 5 years (78.1% vs. 52.9% achieving ≥3-point increase in MFM-32 score).[71] The most common AEs included upper respiratory tract infection, nasopharyngitis, pyrexia, headache, diarrhoea, vomiting, and cough,[69,70] fever and rash were also noted.[65] JEWELFISH is a phase 2, open-label, exploratory trial. Patients included have SMA types 1, 2, or 3 and are between the ages of 6 months and 60 years. These patients have also previously received therapy for SMA including nusinersen and onasemnogene. This study is ongoing and has an expected completion date of 2025. No drug- related safety events have led to withdrawal from JEWELFISH.[65,66,69] RAINBOWFISH is an ongoing, open-label, single-arm, multicenter study. The goal of this study is to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants from birth to 6 weeks of age with pre-symptomatic, genetically diagnosed SMA. Estimated study completion for this trial is 2026.[72]

Investigational therapies

In addition to the therapies outlined, there are other agents being considered in the treatment and management of SMA. Branaplam is a small-molecule RNA splicing modulator that is

thought to increase SMN protein levels. The safety and efficacy of oral branaplam in patients with SMA type 1 is currently being studied. Preliminary data on this medication showed improvement in motor function after 86 days of treatment. Celecoxib has been shown to increase SMN in animal models, and phase 2 and 3 trials are examining use of celecoxib in patients with SMA. The antibiotics azithromycin and the amino-glycoside drug class have possible potential as SMN protein stabilizers. Amino-glycosides have shown possible in vivo efficacy, but toxicity has yet to be investigated. Intrathecal administration of azithromycin in mice exhibited promising data. Bortezomib therapy, though able to improve motor function, has not shown improved survival.[3]

Therapeutic agents not targeting SMN

Many of the medications discussed in this activity focus on SMN-dependent mechanisms of action. However, there can be benefit in therapies that do not utilize SMN-dependent mechanisms in the treatment and management of patients with SMA. Patients with advanced disease or who might require multimodal therapy may benefit from these alternative agents. Myostatin inhibitors are a class of medications that fall under this category. Myostatin is produced in skeletal muscles to inhibit muscle growth. If myostatin is inhibited, patients should be able to gain muscle mass, increase strength, and improve motor function. As muscle weakness is a hallmark symptom of SMA, myostatin inhibitors show promise in the management of patients with SMA. Another mechanism that has been studied is skeletal muscle troponin activation. The agent reldesemtiv has been shown to improve muscle function in patients with SMA through a calcium-sensitizing effect. The result is an increase in the force of muscular contractions in response to nerve activity. Some investigators believe that pyridostigmine, an acetyl cholinesterase inhibitor used in the management of myasthenia gravis, may offer benefit in SMA. Potential benefits include possible increased activation and strength in muscles. Finally, stem cell therapy for SMA has been investigated. Precise recommendations, therapeutic potential, mechanism of action and therapy details regarding this treatment option are still pending.[3]

The effect of SMA on Patients and Families

Traditional management of SMA is associated with significant cost and burden for patients and families, both financially and emotionally. Multiple hospital admissions and appointments are needed with a variety of specialists for the management of breathing difficulties, orthopaedic specialty interventions, speech therapy, specialized nutritional care, and surgeries. Families

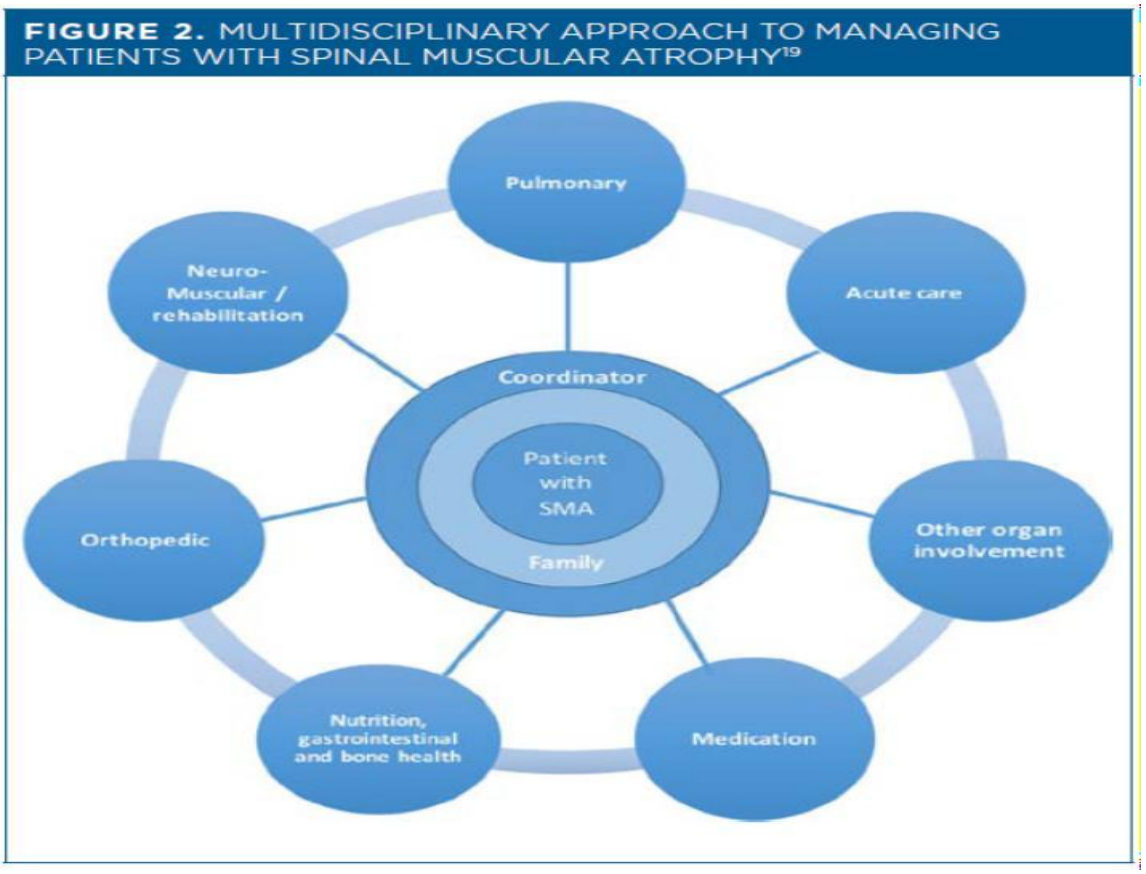
need to maintain ventilators, feeding tubes, suction machines, wheelchairs, back braces, and other resources. Lack of appropriate treatment or interventions could lead to increased patient hospitalizations, with significant financial burden associated with interventions and hospitalizations.[73] Caregivers and the health care system experience additional strain to provide continual care for patients with SMA. One study from 2015 outlined some of the burden families faced prior to the implementation of DMTs.[74] Families reported stress and psychosocial impact of SMA throughout their experiences. First, there was the experience of significant diagnostic delays and the associated frustration from that process. Second, there was the impact of living with SMA. Families needed to confront a number of psychosocial issues associated with an SMA diagnosis, such as coming to terms with a premature death and lost expectations, considering difficult treatments, fear of loss of function, stress, uncertainty, and helplessness.[74] The National Alliance for Care giving found that caregivers for children with rare diseases spend on average 53 hours per week maintaining their care giving responsibilities. This demand often requires caregivers to cut back on working hours, and up to 86% of caregivers for patients with SMA report financial hardship.[73] An economic analysis confirmed the cost burden, both inpatient and outpatient, for patients with SMA is significant and much higher than for healthy counterparts. Patients with infant- onset SMA were found to carry the greatest burden as it correlated with their severe disease. Those with child and juvenile SMA were still found to carry a burden 50-fold higher than their control counterparts. For patients with the most severe disease, the primary driver for cost was inpatient admissions for respiratory infections and respiratory failure. For patients with less severe disease, outpatient expenses, including home health care services, contributed to cost.[73] DMT for SMA is associated with significant financial burden for patients and families; however, pharmacists can assist with access to therapies and mitigating costs. Though these therapies offer new hope for patients and families, their economic value has been debated. Because the clinical trials for SMA therapies have limited numbers of patients, extrapolations were required to conduct economic analyses. Limitations to these extrapolations include variable disease duration in study participants and heterogeneous patient populations. Just 1 economic analysis has examined the impact of newborn screening for SMA. The cost of therapy will remain the same for all patients, but those treated prior to symptom onset may exhibit minimal deterioration or handicaps in the future. Access to these therapies is important for caregivers and patients with SMA. Cure SMA has made its website easy to navigate for patients and families seeking treatment. Nusinersen, onasemnogene, and risdiplam all have dedicated pages on the Cure SMA website. These directories can help patients, caregivers, and

providers navigate some of the logistics associated with these medications. For example, the nusinersen page provides education materials for paediatric and adult patients, insurance policies, payer information, and a map tool to find centres administering nusinersen.[75] For onasemnogene, similar information can be found, including another map tool to facilitate patient access.[76] For risdiplam, payer information and patient education is available.[77]

Accredo Specialty Pharmacy is currently the only specialty pharmacy preparing and shipping risdiplam to patients.[78]

The role of the pharmacist in caring for patients with SMA

A multidisciplinary approach is essential to the management of patients with SMA and is summarized in **Figure 2**.[19] The pharmacist is a key member of any patient care team managing novel or complex medication therapies. In 2016, an article was published discussing many of the key roles a pharmacist plays in caring for patients with diabetes.[79] Many of the key concepts discussed in this article are applicable to pharmacists assisting in the management of patients with SMA, such as the importance of the pharmacist in facilitating and participating in issues surrounding transitions of care, polypharmacy, financial matters, and patient education. Education to patients with SMA and their caregivers should include but is not limited to providing instructions on proper handling and administration of medications, information and resources on the various SMA therapies, expected adverse effects of medication therapies, and expectations of medical care and medication access, as well as any emerging data as new studies become available.



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Handling and Administration

Pharmacists practicing in health systems and specialty pharmacies will need to be aware of the preparation instructions for the current DMTs. Nusinersen must be stored in the refrigerator until use. Once ready to use, the medication vial should be allowed to warm to room temperature without use of any external warming devices. At the time of preparation, nusinersen should be examined to ensure no particulates or discoloration is noted. Each vial is a single-dose vial, and 5 mL should be removed for each dose. Any extra medication in the vial should be discarded. Nusinersen should be administered within 4 hours of preparation (removal from the vial). Filter needles are not needed for the preparation of nusinersen. Sedation needs should be determined by the administering provider. Prior to intrathecal injection of nusinersen, 5 mL of cerebrospinal fluid should be removed from the patient followed by the injection of medication given over 1 to 3 minutes as an intrathecal bolus injection.[30] Onasemnogene is available as a kit for the pharmacy. It is frozen prior to use and must be thawed. Pharmacists have the option of allowing the kit to thaw over 12 hours in the refrigerator or over 4 hours at room temperature. If thawed within a refrigerator, the

medication should be removed from refrigeration on the day of dosing. Once at room temperature, onasemnogene should be a clear to slightly opaque liquid (colour will vary from colourless to faint white). Onasemnogene should always be free from particles. Do not shake onasemnogene at any point in the preparation or delivery process. The medication should be drawn from the appropriate number of vials into a syringe and delivered for infusion in a capped, room temperature syringe to the infusion centre. Onasemnogene must be infused within 8 hours of being drawn into the syringe. If a syringe still contains onasemnogene 8 hours after preparation, both the syringe and medication should be discarded. Pharmacists should not attempt to refreeze onasemnogene after the medication has been thawed. Onasemnogene is administered as a 60-minute intravenous infusion from a syringe.[48] Risdiplam is provided to the pharmacy as a powder for reconstitution. During reconstitution of risdiplam, those preparing the medication should wear gloves and avoid contact with the skin or mucous membranes. Any skin or eye contact with risdiplam should result in washing the area thoroughly. To reconstitute risdiplam, gently tap the bottom of the closed glass bottle to loosen the powder, remove cap, and pour 79 mL purified water into the bottle. Recap the bottle and shake for 15 seconds, then wait 10 minutes. After this time, risdiplam should be a clear solution. If it is not, shake well again for another 15 seconds. Once reconstituted, risdiplam has a 64-day expiration. Pharmacists should make note of this on the bottle and inform patients and caregivers that any unused medication must be discarded after that date. Upon dispensing, the pharmacy should ensure appropriately sized oral syringes are provided to the patient or caregiver.[65] Risdiplam should be stored in the refrigerator. The medication is removed from the bottle with an oral syringe and can be administered by mouth, via gastrostomy tube, or via nasogastric tube. Patients and caregivers should check to ensure there are no large air bubbles and that the correct amount of risdiplam has been drawn up prior to administration. After administration of risdiplam, it is recommended to drink a small amount of water or flush the tube through which the medication was given with a small amount of water in order to ensure all of the medication has been delivered.[80] Risdiplam should be administered once daily after a meal at approximately the same time every day. If a dose is missed, it is recommended that it be administered as soon as possible if still within 6 hours of the dose. If outside the 6-hour window, the dose should be skipped, and the medication should be given at the regularly scheduled time again the next day. If the patient vomits a dose or if a dose is not fully swallowed, patients and caregivers should not administer another dose to make up for lost medication.[65]

Multidisciplinary Care and Medication management

With the advent of DMTs, the need for pharmacist involvement in the care of patients with SMA has only grown. Outside of the management of DMTs, pharmacists managing patients with SMA can participate in reviews of complex medication regimens for patients requiring multimodal supportive care. One aspect where pharmacists can provide oversight is in the review of medication regimens to ensure appropriate bowel schedules are created. Pharmacists can also play a role in the development of nutrition support regimens, including making recommendations on medication interactions with formula and feeding schedules, medication compatibility with feeding tubes, and the provision of total parenteral nutrition. Guidance on the design of efficacious airway clearance treatments and direction of antibiotic therapies are also opportunities for clinical pharmacists to be involved in the care of patients with SMA. Clinical questions surrounding the use of multiple concurrent medications for the management of SMA and comparing the individual SMA agents still exist. Given the variable populations and time frames of the existing clinical data, direct comparisons of SMA agents are difficult to make. In clinical practice, many SMA providers have worked to obtain access to both nusinersen and onasemnogene for their patients. Each medication has a unique mechanism of action, and, as previously discussed, there is the potential for nusinersen therapy to provide additive benefit on top of onasemnogene. Results of the clinical trial investigating this very question are anticipated, but in the meantime, many providers feel as though the potential impact of dual therapy on neuromuscular function is worth fighting to provide. As the first oral agent for SMA, risdiplam has promise to be combined both with SMN DMTs and SMN-independent therapies. The promise of using risdiplam in combination with a medication like nusinersen is the enhancement of full-length SMN expression from combination therapy.[81,82] Pharmacists will continue to play a key role in the oversight of medication selection, dispensing, administration, and monitoring. Select considerations are summarized in Table 3.[30,48,65]

Table 3: Considerations for spinal muscular atrophy medications.

	Nusinersen	**Onasemnogene**	**Risdiplam**
Mechanism	SMN2 directed antisense oligonucleotide	Adeno-associated virus vector-based gene therapy	SMN2 splicing modifier
SMA Indication	Pediatric and adult patients	Age <2 years with biallelic mutations in SMN1 gene	Age ≥2 months

Frequency and route of administration	Initial loading doses then maintenance doses once every 4 months, administered intrathecally	Single-dose intravenous infusion over 60 minutes	Once-daily oral solution
Dosing	12 mg (5ml) per administration 4 loading doses: 3 doses at 14-day intervals; 4th dose administered 30 days after the 3rd dose Maintenance dose: once every 4 months thereafter	1.1×10^{14} vector genomes (vg)/kg of body weight Provides as customized kit to meet dosing requirements Requires systemic corticosteroids for at least 30 days	2 months to <2 years: 0.2 mg/kg ≥2 years, < 20 kg: 0.25 mg/kg ≥2 years, ≥20 kg: 5 mg
Warnings and precautions	Thrombocytopenia and coagulation abnormalities; renal toxicity	Boxed warning: acute serious liver injury Warning and precaution: thrombocytopenia; elevated troponin-l	May cause fatal harm; women of childbearing age should be educated on proper handling
Adverse effects	Later-onset: pyrexia, headache, vomiting and back pain Infantile-onset: lower respiratory infection and constipation	Elevated aminotransferases and vomiting	Later-onset: fever, diarrhoea, rash Infantile-onset: similar to later-onset and upper respiratory tract infection, pneumonia, constipation and vomiting
Drug interactions	N/A	Patient's vaccination schedule may need to be adjusted to accommodate corticosteroid administration	Avoid co-administration with drugs that are substrates of multidrug and toxin extrusion transporters (metformin)

As an SMA provider, it is important to tailor therapy to the individual patient. A neonate with newly diagnosed SMA type 1 is eligible for treatment with onasemnogene and nusinersen. Most providers would want to initiate therapy as soon as possible in this patient with one or both therapies. However, this patient would not be a candidate for risdiplam until older. In contrast, an adult patient with SMA type 4 who initially presented without any symptoms could be managed with watchful waiting until symptoms present. Once symptomatic, this patient would be a candidate for either nusinersen or risdiplam. Either medication could be selected depending upon the patient's needs and preferences. For patients with limited transportation options, or in whom regular procedural sedation may be a risk, risdiplam may be the preferred drug. Some providers may consider fighting for a combination of risdiplam and nusinersen therapy for their adult patients with SMA symptoms. Each patient will present in a unique manner, and therapy should be selected to their exact needs.

Patient Education and Counselling on special considerations

When educating patients and caregivers on the DMTs, each has their own unique counselling points. For nusinersen, it is important to educate on the possibilities of thrombocytopenia, coagulation abnormalities, and potential renal toxicities. Monitoring for these AEs will require additional blood work and laboratory monitoring. Nusinersen also will require on-site administration, coordination of additional transportation, and possible procedural sedation. Patients and caregivers should be made aware of all of these items.[30] For onasemnogene, patients should be educated on the risk of liver injury and the need for laboratory monitoring. This also will involve having additional blood work done. Patients should also be counselled regarding vaccination timing as it pertains to the steroid requirements with onasemnogene. Adjustments to vaccination schedules may be necessary, and viral infections may be more serious during the duration of steroid therapy. Onasemnogene also carries a risk of thrombocytopenia and thrombotic microangiopathy. Both of these should be reviewed with patients and caregivers, and families should be counselled to seek immediate medical attention if patients experience unexpected bleeding, bruising, seizures, and diminished urine output. One important and unique counselling point is that vector shedding will occur through body waste after administration. Caregivers should be counselled on the proper handling of patient faeces after medication administration, including the need to wash hands thoroughly and to double-bag any disposable diapers at the time of disposal.[48] For patients and caregivers being treated with risdiplam, pharmacists should educate patients that the medication may cause foetal harm for women of childbearing age who may come into contact with the medication. Appropriate handling techniques should be reviewed. Male patients should be advised that their fertility may be impacted during treatment with risdiplam. Finally, all patients should be counselled that risdiplam should be a liquid when obtained from the pharmacy, be administered with meals or breastfeeding/bottles, and be administered immediately after being drawn up in the oral syringe.[65]

Coordination of care

Pharmacists can play an important role in the creation of appropriate workflows for administration of these medications at their respective practice sites. This includes both the logistical and financial aspects of utilizing these medications. For example, with intrathecal administration, nusinersen requires coordination of many specialties, including pharmacy technicians for medication preparation; anaesthesia; and lab, operating room, or procedure room staff. Onasemnogene will require coordination with infusion centres regarding

preparation and administration of the medication. Additionally, continued oversight of appropriate monitoring and use of these medications is important. Pharmacists have a key role in ensuring patients meet and receive appropriate laboratory monitoring for continued therapy and that they receive the necessary supportive care, such as prednisolone treatment with onasemnogene.[48]

Impact of COVID-19 Pandemic

The COVID-19 pandemic has impacted many patients with chronic disease states across the care spectrum, including patients with SMA. There have been significant challenges in managing and maintaining the multidisciplinary appointments required for their continued progress. It has been a significant challenge for patients and families to continue to coordinate the care required for management of SMA secondary to appointment restrictions, capacity limitations, and remote evaluations. Interacting with a physical therapist or neurologist via interactive online portals is often not the same as an in-person visit. Additionally, for orthopaedic procedures or coordination of medication infusions or intrathecal injections within the hospital setting, there were temporary restrictions placed on elective procedures in hospitals in early 2020. Those restrictions continued to adjust and change, but no emergent care was downgraded to prioritize the urgency of the pandemic. For paediatric patients requiring hospital admission, many institutions implemented visitor restrictions and limitations, which can be emotionally challenging for patients and families alike. For all patients with chronic diseases, especially those requiring significant respiratory therapy and support, the pandemic has been a source of fear and emotional distress. Logistically and emotionally, the COVID-19 pandemic has made managing the care of a patient with SMA more challenging. Cure SMA has created a corona virus information centre for further information on the pandemic and its impact on families of patients with SMA: https://www.curesma.org/covid19/.

CONCLUSION

SMA is a group of neurodegenerative diseases that have significant impact on patients, families, and caregivers. The burden of SMA spans physical, financial, and psychosocial spheres. Starting in 2016, DMTs entered the market and have since changed the trajectory of this disease. Though there is still a need for clinical trials to compare therapeutic agents, treatment decisions and algorithms are already being devised. Pharmacists can play an integral role in the establishment of access, as well as the initiation, delivery, monitoring, and

administration of these medications.

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