

The Evolution of Disease-Modifying Therapies in Spinal Muscular Atrophy from Palliative to Curative Intent: a Clinical Pharmacy Narrative Review

Sumia Farid^{1*}, Samah Alamin², Nasra Khalfan Alsharji³, Mohd Masih Uzzaman Khan⁴, Ahmed Hameed Alsaedi⁵, Maher Eid Hameed Aloufi⁶, Waleed Mohsen Hadi Murwi⁷, Ahmad Ibrahim Mohammed Alshari⁸, Rania Fahad S. Alwabri⁹, Alia Ameen S. Alrashed¹⁰, Majed Sattam M. Almutairi¹¹, Yaseen Humaidan F. Alrashdi¹², Hezam Awyed Mohammad Almutairi¹³

¹Department of Pharmaceutics, Faculty of Pharmacy, Elrazi University, Khartoum 11115, Sudan

^{2,3}The Royal Hospital, P.O. Box 1331, Postal Code 111, Seeb, Muscat, Sultanate of Oman.

⁴Department of Pharmaceutical Chemistry and Pharmacognosy, College of Pharmacy, Qassim University, Buraydah 51452, Saudi Arabia

^{5,6,7}King Fahad Madinah Hospital, Khaled Bin Al Waleed Branch Road, Al Jamiah-3177, Madinah-42351, Saudi Arabia

⁸Prince Sultan Armed Forces Hospital in Madinah, Ad Difa District, Madinah 42375, Saudi Arabia

^{9,10,11,12}Pharmacy Department, Pharm D, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah-51418, Al-Qassim, Saudi Arabia

¹³Madinah Health Cluster, Ministry of Health, Al Jamiah, Madinah 42351, Saudi Arabia

***Corresponding author**

Dr. Sumia Farid

Department of Pharmaceutics, Faculty of Pharmacy, Elrazi University, Khartoum 11115, Sudan

Email ID:-sema511987@gmail.com

Abstract:

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder, which is characterized by a progressive degeneration of motor neurons attributed to lack of survival motor neuron (SMN) protein. Historically, SMA management was limited to palliative and supportive therapy to enhance the quality of life and minimize the occurrence of complications; however, development of disease-modifying therapies (DMTs) has revolutionized the landscape of therapy for SMA and involves the use of therapies that target the underlying genetic defect. This review aims to provide an extensive insight in the pathophysiology of SMA and clinical manifestations as well as history of treatment strategies with focus on the mechanism, clinical efficacy and limitations of the 3 approved DMTs nusinersen, onasemnogene abeparvovec and risdiplam based on different molecular approaches for increasing SMN protein levels. Furthermore, the need for early diagnosis and in particular newborn screening is developed as a major factor in determining the success of treatment. The growing role of clinical pharmacists in the choice of therapy, monitoring and pharmacoeconomic issues are discussed in this article. Even with these advancements, challenges remain, such as the high cost of therapy, safety concerns over the long term, variability in the response of the patient, and the requirement for combination therapy or medicines that do not depend on SMN, thus highlighting the need for ongoing research and multidisciplinary methods of care.

KEYWORDS:-SMA, DMTs, Nusinersen, Gene Therapy, Risdiplam, SMN Protein & Antisense Oligonucleotides

1..INTRODUCTION

Spinal muscular atrophy is a rare, severe neurodegenerative neuromuscular disorder that is characterized by a wide range of phenotypes, and in its most severe forms is known to cause significant disability and often a short lifespan (Ramdas et al., 2024). Prior to the year 2016, therapeutic interventions were mostly palliative, with the goal of supportive care to manage symptoms and enhance quality of life (Potash et al., 2021). However, recent developments, especially the introduction of gene-based therapies, have greatly changed the course of the disease, requiring a paradigm change in clinical management (Drakou et al., 2025). These novel disease-modifying therapies directly target the underlying genetic defects of SMA and offer the potential to stop or even reverse disease progression due to the targeting of the survival motor neuron gene in an attempt to restore deficient SMN protein levels (Bagga et al., 2024). This therapeutic progression from purely palliative care to disease-modifying care highlights the importance of understanding efficacy and safety profile reasonably in depth by healthcare providers, especially the clinical pharmacists who play an integral role in the SMA care team (Potash et al., 2021). Pharmacists need a thorough knowledge of molecular mechanisms, therapeutic bases, and clinical information behind these therapies to ensure the best patient outcomes and successful treatment strategies (Potash et al., 2021; Virata et al., 2025). This review will, therefore, examine correlation between tissue-level pathology and SMA, give an in-depth understanding of the three currently licensed therapies - preclinical and clinical therapy development and real-world data and supplementary approaches, challenges, and future directions in SMA treatment (Mishra & Mishra, 2025).

Initially classified into different subgroups according to the onset of symptoms and motor function milestones, the historical knowledge about SMA did not consider the paradigm-shifting effect of these modern therapeutic interventions (Proud et al., 2025). The present therapeutic scenario for SMA has now also evolved to include a multidisciplinary approach that incorporates nutritional support, physical therapy, respiratory support, and advanced gene therapy (Ali et al., 2024). This comprehensive strategy has been proven highly effective in promoting survival and motor function milestones for different types of SMA such as pre-symptomatic individuals (Belancic et al., 2025). The introduction of these disease-modifying therapies, such as nusinersen, onasemnogene abeparvovec and risdiplam, represent a major change in the treatment of SMA, moving away from supportive care and focusing on the genetic deficiency itself (Bagga et al., 2024; Li et al., 2023). Specifically, nusinersen, which is an antisense oligonucleotide, regulates SMN2 splicing, onasemnogene abeparvovec, which delivers a functional SMN1 gene using an adeno-associated viral vector, and risdiplam, which is a small molecule, which also targets SMN2 pre-mRNA (Badina et al., 2024; Proud et al., 2025; Tsai et al., 2024). Each of these different pharmacological interventions attempts to increase the levels of functional SMN protein by either altering the splicing of the SMN2 gene or by direct replacement with the SMN1 gene in an attempt to treat the basic molecular deficiency that defines SMA (Corti et al., 2025). Nusinersen specifically, increases the production of full length of SMN protein by modulation of SMN2 gene splicing, which has shown improvement of the muscle function and survival rate, but requires periodic intrathecal administration (Xu et al., 2024). Onasemnogene abeparvovec, on the other hand, is a one-time gene treatment for pediatric patients younger than two years, which is done using a modified adeno-associated virus to apply a functioning version of the SMN1 gene, which helps in production of the SMN protein over long periods of time (Abati et al., 2024).

2.UNDERSTANDING SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder that is characterized by the degeneration of alpha motor neurons of the spinal cord and the brain stem causing progressive muscle weakness and atrophy (Przymuszala et al., 2022). This degeneration is largely due to a lack of a protein called survival motor neuron, which is coded for by a gene called SMN1 (Motyl and Gillingwater, 2022). While humans have a gene that has been duplicated, SMN2, due to differential splicing, usually produces an unstable, shorter protein isoform that is dysfunctional and unable to compensate for the absence of SMN protein functional from SMN1 (Sanmaneechai et al., 2023). The number of SMN2 gene copies is inversely

related to the severity of the disease, that is, people with more SMN2 copies generally suffer less from the disease SMA due to more production of partially functional SMN protein (Stettner et al, 2023). This molecular insight serves as the foundation for the therapeutic approaches used by current disease-modifying agents, which are mostly based on increasing SMN functional protein levels either by upregulating SMN2 expression or by replacing the deficient SMN1 gene (Kotulska et al., 2021). For example, nusinersen and risdiplam are splicing modifiers, which increase exon 7 inclusion in the SMN2 transcript to generate more full-length and functional SMN protein (Day et al., 2022; Wiedmann & Cairns, 2023). Onasemnogene

abeparvovec, however, uses a different mechanism of administering the functional SMN1 gene by an adeno-associated virus type 9 vector, therefore allowing the generation of the SMN protein in a sustained manner (Strauss et al., 2022). Nusinersen, the first antisense oligonucleotide, requires repeated intrathecal administration, because it cannot pass the blood-brain barrier, and risdiplam, a small molecule, provides oral administration and systemic distribution (Kirschner, 2021). Conversely, onasemnogene abeparvovec is a single-dose gene therapy, where the functional SMN1 gene is directly inserted into the motor neuron cells using an adeno-associated virus type 9 vector in order to provide a long-term expression of SMN protein (Mendonça et al., 2023).

3. PATHOPHYSIOLOGY OF SMA

SMA is mainly caused by bi-allelic mutations in the SMN1 gene with consequent reduction in the amount of an important protein (the survival motor neuron protein) for motor neuron function and survival (Crisafulli et al., 2023). However, the presence of the SMN2 gene, a paralog of SMN1, to some extent counteracts the severity of the disease, because it generates a limited amount of functional SMN protein through alternative splicing (Hatanaka et al., 2024). This variable splicing pattern in SMN2 leads to exclusion of exon 7 resulting in a truncated and unstable protein isoform; however, a small percentage of transcripts include exon 7, producing a full-length and functional SMN protein (Mendonça et al., 2024). Consequently, the number of copies of the SMN2 gene is directly modulating the clinical phenotype of SMA, and in general, the higher the number of copies, the better the functional production of SMN protein and the lower the severity of the disease (Eshrif et al., 2023; Vill et al., 2024). This understanding is the basis of therapeutic interventions, which focus on the exon 7 inclusion of SMN2 to be improved, or even the direct replacement of the defective SMN1 gene (Chiriboga et al., 2024). The three currently approved therapies for SMA, nusinersen, risdiplam and onasemnogene abeparvovec, target this basic SMN protein deficiency by utilizing different molecular mechanisms (Gowda et al., 2023). In particular, nusinersen and risdiplam work by increasing the production of SMN protein by altering the splicing of SMN2. Specifically, nusinersen and risdiplam act by increasing SMN protein production by modifying SMN2 splicing while onasemnogene abeparvovec introduces a functional SMN1 gene (Alstyne et al., 2021; Costamagna et al., 2022; Shell et al., 2023; Strauss et al., 2022).

Nusinersen is an antisense oligonucleotide which specifically targets an intronic splicing silencer called N1 element in intron 7 of SMN2 gene thereby augmenting exon 7 inclusion and increasing full length SMN protein expression (Zhou et al., 2022). However, another orally administered small molecule, risdiplam, also induces the inclusion of exon 7 in SMN2 pre-mRNA, which affects splicing, resulting in higher systemic levels of SMN protein (Kokaliaris et al., 2024; Sliwinska & Rakus-Kwiatosz, 2023). Onasemnogene abeparvovec (gene therapy), in which a functional gene SMN1 is delivered with an adeno-associated virus vector, restoring the SMN protein production in motor neurons. This genetic heterogeneity and the variety of the mechanisms of action of approved therapies highlight the complexity of SMA pathogenesis and the individual courses of treatment required for optimal treatment of patients. Furthermore, there is still ongoing research attempting to determine other exonic and intronic SMN2 variants that may have a role in SMN2 splicing efficiency, which may explain the observed phenotypic variability in SMA patients despite similar SMN2 copy numbers (Zambon et al., 2024).

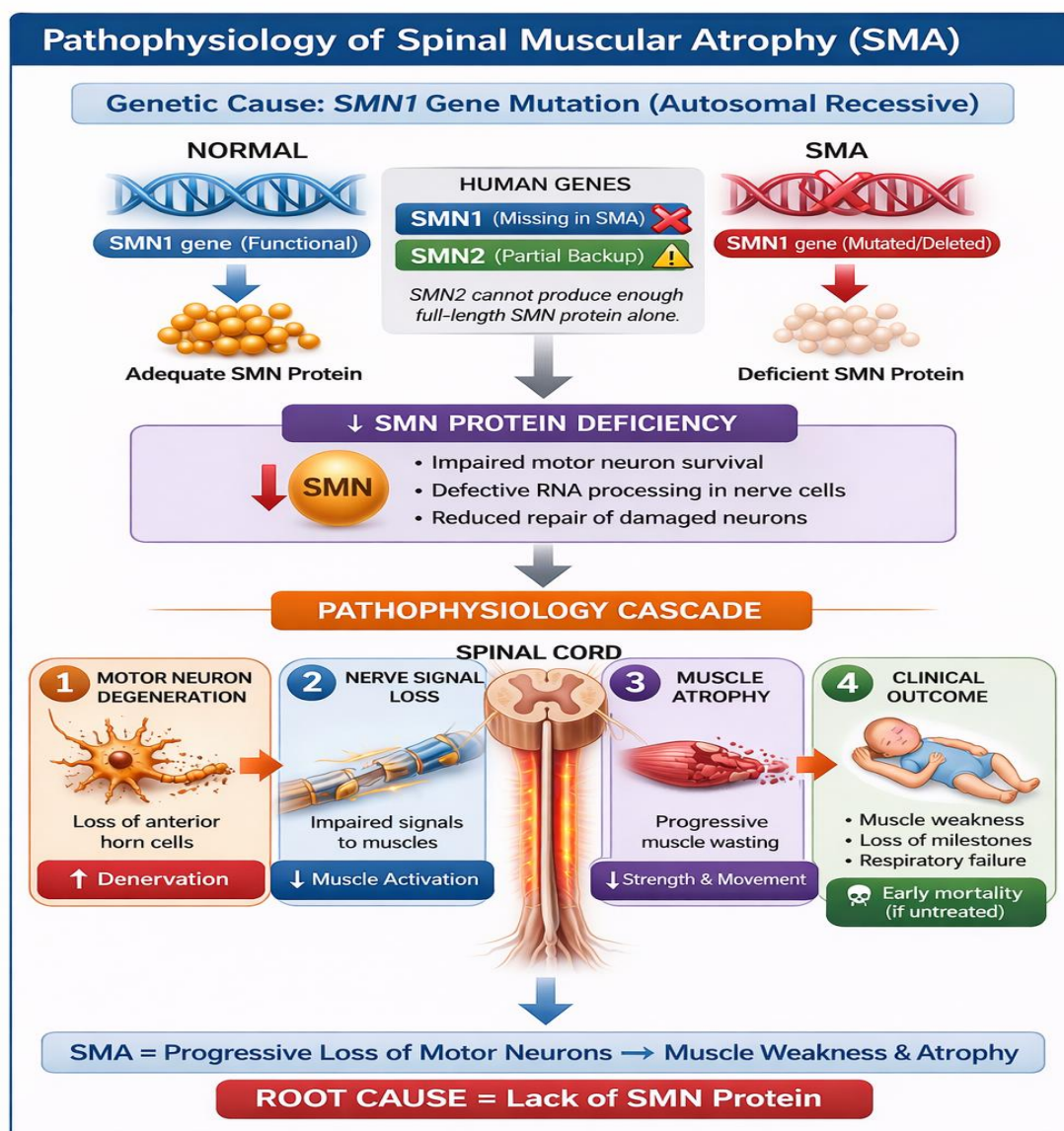


Figure 1: SMN1 gene loss leads to SMN protein deficiency and progressive motor neuron–driven muscle weakness.

The emergence of treatments like nusinersen, risdiplam and onasemnogene abeparvovec is a major paradigm shift in the management of SMA, shifting from symptomatic and supportive care to disease-modifying interventions (Antonaci et al., 2023; Hassan et al., 2022). Nusinersen as the first approved therapy paved way for subsequent therapies as it demonstrated efficacy of targeting SMN2 splicing for increased SMN protein levels (Savini et al., 2021; Veerapandiyani & Duvuru, 2024). On the other hand, risdiplam, a small molecule, when taken orally, also promotes exon 7 inclusion in SMN2 pre-mRNA through a splicing modification, and results in higher levels of SMN protein systemic (Masson et al., 2022). Onasemnogene abeparvovec, meanwhile, delivers a fully functional copy of SMN1 gene into motor neuron cells directly using an adeno-associated virus 9 vector to overcome SMN protein deficiency through gene replacement (Leon-Astudillo et al., 2022). Nusinersen, a modified antisense oligonucleotide, specifically binds to an intronic splicing silencer, N1 element, which is present in intron 7 of SMN2 pre-mRNA that's responsible for preventing splicing repressors from binding, hence promoting the inclusion of exon 7 (Qiu et al., 2022). This mechanism ultimately results in the production of higher levels of normal length, fully functional SMN protein (Sun et al., 2022). In contrast, risdiplam, an orally bioavailable small molecule, directly interacts with two regions of SMN2 pre-mRNA in order to promote the recruitment of the U1-snRNP1 particles to the splice donor site of intron 7, which promotes exon 7 inclusion (Rashid & Dimitriadi, 2024). Finally, onasemnogene abeparvovec is a direct delivery of a working SMN1 gene into the target cells using an adeno-associated virus serotype 9 vector, which helps to continuously produce SMN protein (YUCSEL & YUKSEL, 2023). Although

the introduction of these therapies has revolutionized the treatment of SMA through boosting SMN protein levels, they are not a complete cure, thus pointing to the possible need for combination therapies or innovative therapies to further enhance results (Butchbach & Scott, 2022)

4. CLINICAL MANIFESTATIONS AND DISEASE PROGRESSION

Spinal Muscular Atrophy is a group of diseases that have a spectrum of clinical phenotypes which are mainly defined by progressive muscle weakness and atrophy caused by the degeneration of alpha motor neurons in the spinal cord and brainstem. The severity and age of onset of SMA is highly variable ranging from the severe infantile onset with profound weakness and respiratory failure to milder adult onset with subtle motor deficit (Brakemeier et al., 2024; Mizuno et al., 2023). Historically, SMA has been described in four types according to age of symptom onset and achieved motor milestones, however with the advent of disease modifying therapies, a more complex method of describing the disease, dependent on SMN2 copy number and functional abilities (e.g. non-sitter, sitter, walker) has developed to better reflect disease course and response to treatment (Curry et al., 2024). This changing concept of SMA classification is important in guiding the personalised approach to therapies as the number of copies of SMN2 is directly related to the amount of functional SMN protein produced and therefore the potential efficacy of interventions that target SMN2 (Babić et al., 2023; Bjelica et al., 2023). For example, patients with a lower number of SMN2 copies tend to have a more severe phenotype and therefore need to be treated earlier and potentially more aggressively (Fernandes et al., 2024). Beyond the pathology of motor neurons, SMA is now known to be a multi-systemic disorder with implications for different organs of the body, such as the cardiovascular, gastrointestinal and respiratory systems, which further complicates the management of this disorder in patients (Zhang et al., 2025). The success of these therapies in ameliorating motor neuron degeneration has consequently led to a better clinical recognition of other systemic manifestations of motor neuron degeneration and calls for comprehensive, multidisciplinary care. Before disease-modifying treatments were introduced, SMA was the number one genetic cause of infant mortality with the severe forms leading to premature death or lifelong ventilation (Day et al., 2021). SMA is a clinically heterogeneous disorder, with clinical severity and maximum motor function reaching, grouped into types 0-4, depending on the age of onset, clinical severity and maximum motor function reached, with Type 0 being the most severe and presenting prenatally or at birth, and Type 4 presenting in adulthood with mild proximal weakness (Cook et al., 2025; Ribero et al., 2023). Specifically, Type 0 SMA often results in the death of the fetus or neonate, while Type 1, the most common type in babies, usually results in death within two years due to respiratory insufficiency if not treated (Abati et al., 2022; Burr & Reddivari, 2021; Sutherland et al., 2021).

5. TRADITIONAL PALLIATIVE CARE IN SMA MANAGEMENT

Historically, the treatment of SMA was aimed at supportive and palliative care because of the lack of disease-modifying therapies (Alotaibi et al., 2024). This approach focused mainly on relieving the symptoms, preventing the complications and enhancing the quality of life for the patients with interventions like providing respiratory support, nutritional management and physical therapy (Pan et al., 2023). Palliative care involved the multidisciplinary team approach to manage neurological, orthopedic, gastrointestinal, and respiratory complications (Chrastina & Harokova, 2025). Prior to the advent of disease-modifying therapies, respiratory issues, including loss of ability to cough properly, low oxygen levels in the blood, and recurrent infections, were the primary cause of morbidity and mortality among SMA patients (Edinoff et al., 2021). As such, much of the management strategies focused on interventions such as non-invasive ventilation, assisted coughing techniques, and preventive treatment of respiratory infections to preserve survival and quality of comfort for the patient (Ali et al., 2024; Paracha et al., 2021). Nutritional support, often including gastrostomy tube placement, was important for treating the problem of dysphagia and preventing aspiration which is common in the more severe types of SMA (Charlotte, 2023).

Table 1: Supportive Therapies and Limitations in Spinal Muscular Atrophy.

Category	Key Aspect	Description (with References)
Supportive Therapies and Symptom Management	Treatment Goal	Focused on reducing the impact of progressive muscle weakness, particularly in Type 1 SMA with severe respiratory and feeding difficulties (Charlotte, 2023; Sanmaneechai et al., 2024).
	Family-Centered Decisions	Management ranged from palliative care to intensive interventions such as ventilation and gastrostomy, depending on family preferences (Chan et al., 2022).
	Prognosis (Pre-therapy era)	Poor quality of life and life expectancy typically <2 years in Type 1 SMA infants (Chiriboga et al., 2023; Paracha et al., 2021).
	Need for Advancement	Emphasized the need for therapies that modify disease progression rather than only manage symptoms (Boursange et al., 2022; Magelssen et al., 2021).
	SMN-Augmenting Therapies	Introduced a paradigm shift with potential to alter disease course and improve long-term outcomes (Abati et al., 2024).
	Respiratory Support	Early mechanical ventilation improves pulmonary function and quality of life (Yao et al., 2021).
	Non-Invasive Ventilation (NIV)	Frontline therapy that manages ventilatory abnormalities and prolongs survival in less severe cases (Lagae et al., 2024).
	Airway Clearance Techniques	Chest physiotherapy and mechanical insufflation-exsufflation help prevent infections and manage secretions (Potash et al., 2021).
	Proactive Respiratory Care	Continuous monitoring of cough effectiveness and nocturnal hypoventilation is essential (Potash et al., 2021).
	Nutritional Support	Gastrostomy tube placement improves survival and quality of life (Baranello et al., 2021; Piastra et al., 2025).
	Overall Impact	Comprehensive supportive care improved survival even before disease-modifying therapies (Baranello et al., 2021).
	Lack of Curative Potential	Does not address the underlying genetic defect of SMA (Buchignani et al., 2025).
	Disease Progression	Continued motor decline and reduced life expectancy despite supportive care (Buchignani et al., 2025).

Limitations of Palliative Approaches	Developmental Outcomes	Infants rarely achieve motor milestones and often do not survive beyond 2 years (Cancés et al., 2022).
	Limitations of NIV	Response to ventilation and disease-modifying therapies remains variable and unpredictable (Abati et al., 2024; Lagae et al., 2024).
	Decision-Making Complexity	Requires careful discussion with families regarding risks, benefits, and expectations (Abati et al., 2024).
	Continued Need for Palliative Care	Remains relevant for severely affected patients despite newer therapies (Lagae et al., 2024).
	Advanced Case Management	Severe cases may still require tracheostomy and long-term mechanical ventilation (Piastra et al., 2025).
	Overall Limitation	Highlights ongoing challenges in managing advanced SMA in the modern therapeutic era (Piastra et al., 2025).

6. EMERGENCE OF DISEASE-MODIFYING THERAPIES (DMTS)

The advent of disease-modifying therapies has fundamentally changed the clinical landscape of SMA management, bringing to clinical practice treatments that address the molecular basis of SMA disease, rather than simply ameliorating the symptoms of SMA. These novel treatments such as gene therapies and antisense oligonucleotides directly affect the production or function of the survival motor neuron protein, and thus aim to stop or reverse neurodegeneration and increase motor function (Tavares et al., 2024). Specifically, three types of therapies have received approval by the FDA and European Union and are classified as SMN upregulators or correctors, which directly target the SMN-deficiency that is inherent in SMA (Day et al., 2022). These include nusinersen, an intrathecally administered antisense oligonucleotide; onasemnogene abeparvovec, an intravenously administered gene replacement therapy; and risdiplam, an orally administered SMN2 splicing modifier (Cancés et al., 2022). These novel pharmacological interventions, through their action on the genetic faults, represent a major step away from previous palliative care approaches, showing a significant improvement in survival, motor milestones and respiratory function, especially when treatment is started early (Alves et al., 2024; Gulati et al., 2025; Saposnik et al., 2022).

6.1. Nusinersen: Mechanism of Action and Clinical Efficacy

Nusinersen is an antisense oligonucleotide that helps to regulate the splicing of SMN2 gene to produce full-length and functional SMN protein (Ramdas et al., 2024). This is directly connected to the genetic deficiency that is characteristic of 5q spinal muscular atrophy, which is where gene mutations result in the individual having insufficient levels of the critical SMN protein (Piastra et al., 2025). By promoting the inclusion of exon 7 in SMN2 pre-mRNA splicing, nusinersen essentially brings the balance in favor of more SMN protein being produced, and in a fully functional form, that is required for the survival and function of motor neurons. This molecular intervention has been very clinically effective in patients of widely varying ages and SMA types, which explains its approval for use by the U.S. in 2016 and the E.U. in 2017 (Day et al., 2022). Nusinersen being intrathecal every four months, it is guaranteed to reach the central nervous system and is able to perform its function of promoting the expression of SMN (Kotulska et al., 2022; Saramak & Szejko 2024).

This targeted delivery method is important in light of the fact that SMA predominantly targets the motor neurons in the spinal cord, making it important to have direct access to the cerebrospinal fluid for maximal therapeutic effect (Paracha et al., 2021). Beyond nusinersen, there are other therapeutic agents such as risdiplam that is an orally administered small molecule drug, which is also considered an SMN2 splicing modifier to increase functional SMN protein levels (Badina et al., 2024; Bjelica et al., 2024). Another approach to treatment is gene replacement (onasemnogene abeparvovec) which adds a working copy of the SMN1 gene into motor neurone cells (Bashiri et al. 2021). The efficacy of these SMN-dependent treatments both SMN1 gene replacement and SMN2 pre-mRNA splicing modulation are greatly increased when done pre-symptomatically highlighting the importance of SMA newborn screening programmes (Oskoui et al., 2021). These therapeutic advancements signify a paradigm shift in the management of SMA which has been traditionally been managed with supportive care only but with the advent of these therapies it is now

managed with a therapeutic intervention that actually modifies the disease course at its molecular origin (Bagga et al., 2024). Nusinersen in particular is a 2'-O-methoxyethyl phosphorothioate modified drug that works by blocking the splicing factors and therefore increasing the exon 7 inclusion in SMN2 mRNA transcripts and increases the production of full-length SMN proteins (Edinoff et al., 2021).

6.2 Onasemnogene Apeparvovec: Gene Therapy Approach

Onasemnogene apearvovec is a different type of therapy, which uses an adeno-associated virus 9 vector to deliver a functioning version of the SMN1 gene directly to motor neurons (Li et al., 2023; Przymucha et al., 2022). This is a one-time intravenous administration in patients younger than two years of age, which is supposed to cover the genetic defect by allowing the production of the essential SMN protein to be sustained (Fox et al., 2022; Tsai et al., 2024). This gene therapy approach is aimed at the root cause of SMA, by introducing the required genetic blueprint to produce the endogenous SMN protein, in contrast to SMN2-targeting therapies that target the alternative splicing of the SMN gene to produce more functional SMN protein (Badina et al., 2024). Unlike nusinersen, which needs intrathecal injections repeated regularly, onasemnogene apearvovec's single systemic injection is intended to be of long-term therapeutic use by transducing motor neurons throughout the body (Sleigh et al., 2023). This approach, while having the potential to provide long-lasting efficacy, comes with the considerable cost of up-front costs, as well as, the need to consider the long-term safety profile and immunological responses of the vaccine. Real-world evidence and pivotal randomized-controlled trial confirm that onasemnogene apearvovec is significantly associated with better survival rates and motor function milestones in patients with Type 1 and Type 2 SMA, which often result in some of these achievements: independent sitting and prolonged ventilator-free survival (similar to the results observed with nusinersen and risdiplam; Ali et al., 2021; Belančić et al., 2025; Proud et al., 2025).

6.3 Risdiplam: Oral SMN2 Splicing Modifier

Risdiplam is a small molecule for oral administration that acts as an SMN2 splicing modifier, increasing the inclusion of exon 7 of SMN2 mRNA transcripts that then increases the production of full-length, functional SMN protein (Corti et al., 2025). As the first orally available therapy for SMA, risdiplam carries a major advantage in accessibility to the patient as well as low invasiveness when compared with injectable treatments (Motyl & Gillingwater, 2022; Singh et al., 2021). This systemic delivery mechanism guarantees wide bio-distribution of the drug, which may get into peripheral tissues as well as the central nervous system to improve the multifaceted manifestations of SMA (Wiedmann & Cairns, 2023). Clinical trials have shown the efficacy of risdiplam in improving the motor function and survival of patients with different types of SMA and ages including pre-symptomatic infants with many achieving their motor milestones such as independent sitting and standing (Zanoteli et al., 2024). Moreover, indirect treatment comparisons indicate that onasemnogene apearvovec may be associated with better efficacy compared to both nusinersen and risdiplam in some of the outcomes but with caution, this should be interpreted with caution due to methodological limitations and lack of direct head-to-head trials (Blair, 2022). However, the single dose nature of onasemnogene apearvovec, which could be a source of superior efficacy, must be compared against its significant financial burden and the practical difficulties linked to antibody screening and potential transaminitis (Bagga et al., 2024). Despite these considerations, all three approved disease-modifying therapies - nusinersen, risdiplam, and onasemnogene apearvovec - have made significant changes to the natural history of type 1 SMA, allowing children to reach motor milestones that were previously impossible (Kokaliaris et al., 2024).

While all three treatments have shown great potential for therapy, their unique mode of operation, mode of administration, and cost-effectiveness profile require careful consideration in clinical decision making. Risdiplam, in particular, is a huge step forward in evolution by enabling a non-invasive treatment option that enables more of the survival motor neuron full-length protein to be produced by modulating SMN2 splicing (Chiriboga et al., 2023; Sanmaneechai et al., 2023). This oral SMN2 splicing modifier is authorised for use in patients of a broad age range and SMA types (Paracha et al., 2021). This accessibility and the possibility of crossing the blood-brain barrier and targeting central and peripheral organs makes risdiplam a versatile option for SMA management (Bashiri et al., 2021). The existence of three different disease modifying therapies for SMA, nusinersen, onasemnogene apearvovec and risdiplam, reflects the fast-paced development in disease modifying therapies for this neurodegenerative disorder (Strauss et al., 2022).

7. CLINICAL PHARMACY'S EVOLVING ROLE IN SMA TREATMENT

This proliferation of medication choices requires a complex understanding of the pharmacokinetics, pharmacodynamics, and potential drug interactions of each drug by clinical pharmacists in an effort to optimize patient outcome. Furthermore, pharmacists are an important part of counseling on the specific considerations of administration, adverse effect profiles and monitoring parameters associated with each therapy, including potential for hepatic toxicity and thrombotic microangiopathy with onasemnogene abeparvovec (Waldrop et al., 2023). Given the complex and individual nature of SMA treatment, clinical pharmacists are also instrumental in the complex world of health economics, such as insurance coverage, managed care protocols, and value-based payment models for such high-cost therapies (Potash et al., 2021). Their knowledge of medication management, patient education, and interprofessional collaboration make them an important stakeholder in the appropriate access and adherence to, and outcomes from, individuals receiving these life-changing treatments for SMA. The diverse administration routes and coverage mechanisms [oral therapies under pharmacy benefits, and injectable or one-time infusions under medical benefits] do have unique challenges for managed care pharmacists in ensuring equitable access and minimizing fragmented care (Potash et al., 2021).

Table 2: Patient Selection, Treatment Initiation, and DMT Management in Spinal Muscular Atrophy.

Section	Key Aspect	Description
Patient Selection and Treatment Initiation	Personalized Treatment Approach	Treatment selection is based on patient-specific factors such as age, disease severity, SMN2 copy number, and prior treatment response (Potash et al., 2021).
	Dynamic Treatment Paradigm	Shift from fixed sequential therapy to personalized regimens with continuous reassessment of effectiveness (Voigt-Muller et al., 2025).
	Early Treatment Strategy	Immediate pharmacotherapy is recommended for infants with ≥ 4 SMN2 copies to improve prognosis (Potash et al., 2021).
	Presymptomatic Intervention	Early treatment in presymptomatic infants significantly improves motor and survival outcomes (Strauss et al., 2022).
	Guideline Recommendations	Pharmacotherapy should begin as early as possible in all SMA types to prevent irreversible neuronal and muscle degeneration (Potash et al., 2021a; Potash et al., 2021b).
	Importance of Early Diagnosis	Early diagnosis and intervention are critical to preserving motor function and preventing neuronal loss (Potash et al., 2021).
	Paradigm Shift	Transition from palliative care to early disease-modifying interventions requiring refined clinical strategies (Drakou et al., 2025).
	Limitations of Traditional Classification	Traditional SMA subtypes based on age and milestones are insufficient in the era of disease-modifying therapies (Proud et al., 2025).
	Genetic-Based Stratification	Patient selection now relies on genetic markers (e.g., SMN2 copy number) and symptom status rather than phenotype alone (Corti et al., 2025; Strauss et al., 2022).

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	Emerging Genetic Modifiers	Additional modifiers such as PSL3 are under investigation to refine therapeutic decision-making (Querin et al., 2023).
Dosing, Administration, and Monitoring of DMTs	Pharmacokinetic Variability	DMTs show variability in PK/PD, requiring precise dosing and adherence to protocols (general concept from section).
	Individualized Drug Considerations	Requires evaluation of drug-drug interactions, organ function (renal/hepatic), and genetic polymorphisms (general concept).
	Nusinersen Administration	Intrathecal delivery requires consideration of CSF dynamics and challenges in patients with spinal deformities (Veerapandiyar & Duvuru, 2024).
	Systemic Therapies	Treatments like onasemnogene abeparvovec and risdiplam require monitoring for systemic toxicities (e.g., liver and hematologic effects) (Zambon et al., 2024).
	Safety Monitoring	Close pharmacovigilance is essential due to potential off-target effects and adverse reactions (Zambon et al., 2024).
	Timing of Therapy	Delayed administration of onasemnogene abeparvovec in advanced SMA Type 1 is associated with fatal outcomes (Pongsakornkullachart et al., 2025).
	Importance of Early Intervention	Early initiation maximizes therapeutic benefits and reduces risks (Shell et al., 2023).
	Lack of Comparative Data	Limited head-to-head evidence complicates optimal treatment selection (Antonaci et al., 2023).
	Research Gaps	Need for clinical trials and real-world evidence to guide sequencing and combination therapies (Mishra & Mishra, 2025).
	Limitations of Current Therapies	Not all patients respond adequately to SMN-enhancing therapies (Cook et al., 2025).
	Future Directions	Development of SMN-independent therapies is needed for improved outcomes (Cook et al., 2025).

8.Management of Adverse Effects and Drug Interactions

The long-term safety profiles of these advanced therapeutics are under development with the need for close monitoring for both known and unexpected adverse events especially in the context of combination therapies or sequential therapy regimens (Leon et al., 2022). This means having robust pharmacovigilance policies in place and effective post-market surveillance systems in place to detect adverse effects that may be rare or delayed and ensure the safety and efficacy of these treatments. This includes having robust pharmacovigilance strategies in place and effective post-market surveillance systems in place to identify any adverse effects that may be rare or delayed and to ensure the safety and efficacy of these treatments (Kwon et al., 2025). In addition, the interventional treatment of complications related to treatments, e.g. the implantation of cerebrospinal fluid reservoirs for frequent intrathecal injections or the implantation of a spinal for scoliosis, underline even more the complexity of comprehensive SMA care. The subtle routes of

administration of such therapies, e.g., intrathecal delivery of nusinersen, entail inherent risk, like raised intracranial pressure and complications that require intubation of the patient that requires specialized clinical expertise while rendering treatment (Leon-Astudillo et al., 2022). For example, while it's well-researched that intrathecal administration of nusinersen is highly beneficial, the procedure is not without complications, which is why having trained practitioners is important, as is having lots of post-procedure care. The insufficiency of current SMN-dependent therapies demonstrates the need for the development of combinatorial therapies that target other molecular pathways involved in SMA pathophysiology including the mitochondrial dysfunction and cell death pathways (Basak et al., 2024). Additionally, exploring novel methods of gene expression modulation, i.e., based on RNA, small molecules, and gene editing, shows promise for optimizing the management of SMA in addition to SMN2 modulation (Virata et al., 2025).

Such advancements, especially those that are SMN independent targets, are important considered that SMN2 modifying therapies, although transformative, do not fully restore SMN levels to the levels seen in healthy subjects (Hatanaka et al., 2024). Despite major breakthroughs in therapy, there are limitations, as is shown by some serious side effects such as headache, back pain, liver and heart damage as well as the possibility of forming an anti-AAV9 antibody, which may reduce the success of the therapy and increase the risk of an immunological reaction (Basak et al., 2024). Furthermore, possible complication of repeated intrathecal administrations of some therapies such as infections or cerebrospinal fluid leak requires to create alternative methods of administration that are less invasive (Guo et al., 2024). Moreover, while some patients experience a remarkable improvement, there are still many of them who require significant supportive care, such as the need for breathing assistance and feeding support, highlighting the ineffectiveness of the existing treatments in their effort to completely reverse the course of the disease (Przymuszala et al., 2022).

Consequently, the structural changes on the retina demonstrated in non-clinical studies with some therapeutic agents, if not already demonstrated in clinical SMA cohorts, require long term vigilance and further investigation into long term ophthalmic safety (Day et al., 2022). The constant need for holistic approaches apart from the pharmacological approach gives more importance to the role of physical therapy, occupational therapy and nutritional support in the process of maximizing patient outcomes and improving quality of life in general (Badina et al., 2024). This constant need serves as an indicator to the complex multi-organ system involvement of SMA and how current treatments although a transformation are not a complete cure (Roos et al., 2024). Instead, these disease modifying therapies form a basis for the prevention of irreversible neurological damage and better patient outcomes with a focus on transitioning from a palliative to a curative intention paradigm in SMA management (Servais and Moreno 2024). Despite these huge advancements, it is the tremendous economic burden of these novel therapies that makes the case for their inclusion in newborn screening programmes to maximise their therapeutic impact and ensure equitable access (Bagga et al., 2024). These financial considerations combined with the complexities of long-term monitoring and possible negative effects, emphasize the importance of conducting detailed health economic analyses and effective healthcare policies to enable sustainable access and the best use of these transformative treatments.

9. Pharmacoeconomic Considerations and Access to Care

The high cost of disease modifying treatments for SMA, combined with uncertainties about the long-term efficacy and safety of the therapies, poses significant challenges for healthcare systems and payers across the world (Skedgel, 2021). This requires stringent pharmacoeconomic studies on cost-effectiveness and reimbursement, especially with the potential of these treatments to radically change the prognosis of SMA in combination with newborn screening programmes [Dangouloff et al., 2021; Kotulska et al., 2021]. The introduction of newborn screening of 5qSMA is important to enable early, presymptomatic therapeutic intervention, despite existing gaps in our understanding of outcomes for some genetic subgroups such as those with four copies of SMN2 (Mendell et al., 2021; Vill et al., 2024). However, the total financial costs that are attached with SMA management, such as hospitalization, direct costs are substantially reduced when patients are identified with early screening and get timely treatment (Dangouloff et al., 2022). While newborn screening is a very important step in the journey towards optimizing outcomes, the economic evaluation of these therapies is complicated by the difficulty in demonstrating long-term efficacy and the use of traditional cost-effectiveness thresholds for orphan drugs for rare diseases (Paracha et al., 2021). Indeed, while several studies suggest that the incremental cost-effectiveness ratio is unsustainable for all three approved SMA drugs when looking at symptomatic treatment, cost savings and better health outcomes are seen when used for presymptomatic treatment, which suggests the economics of early intervention (Lim et al., 2024).

10. TRANSITION FROM PALLIATIVE TO CURATIVE INTENT

This paradigm shift is supported by the unprecedented capacity of disease-modifying therapies to not only reduce disease progression but to seriously modify the natural history of SMA, changing the paradigm of symptomatic management of SMA to treating the underlying genetic defect. This basic shift in therapeutic approach has led to SMA being transformed from a universally fatal disease to a manageable, albeit still difficult, chronic disease (Nishio et al., 2023). This change in the model of care from a palliative to a disease modification approach has significant implications for patient outcomes, healthcare resource utilization and long-term societal burden associated with SMA. The economic burden of SMA, both direct and indirect costs, is significantly affected by the introduction of newborn screening programs and early therapeutic intervention that can lead to significant reductions in the overall healthcare costs related to the disease (Dangouloff et al., 2021; Yaftian et al., 2024). For example, economic analyses have established the cost-effectiveness of newborn screening and gene therapy showing an economic value for universal newborn screening in jurisdictions where disease-modifying therapies are available (Chan et al., 2022; Groulx-Boisin et al., 2023).

The early detection of SMA through newborn screening and subsequent access to disease-modifying treatments to the infant has a significant impact on the burden experienced by caregivers due to the reduction in productivity losses, healthcare resource consumption, and out-of-pocket costs (Jimenez et al., 2022). This proactive approach not only helps to improve the motor and the overall developmental milestones for the affected infants and children, but it drastically lowers the significant disability and high mortality rates that were previously linked to SMA (Chan et al., 2022). Consequently, the improved motor function and the increased survival rates that result from early intervention translate into a significantly extended and better quality of life for individuals with SMA and this is often at par with the general population (Weidlich et al., 2023). This early intervention also results in a significant decrease in the massive use of healthcare resources that was the hallmark of the management of SMA before the advent of these therapies (Weidlich et al., 2023). Moreover, the positive effect of treatment is even extended to the reduction of medical costs for symptomatic patients with two or three SMN2 copies, despite the overall higher costs due to the prohibitive price of the treatments themselves (Dangouloff et al., 2022). However, whilst direct medical costs may be high, especially as they are for gene therapies, these are more than recovered by savings in the indirect costs of long term care and management of chronic conditions, illustrating the complex nature of the economic burden of early treatment (Paracha et al., 2021).

Despite the transformative potential of these therapies, sustained long-term management and rigorous follow-up protocols are imperative to monitor for delayed adverse events, assess durable efficacy, and address evolving patient needs. The lack of long-term data of comprehensive information about prolonged life expectancy and outcome for patients treated with therapies such as Spinraza or Zolgensma, together with the unpredictable nature of the phenotypic severity, requires ongoing research (Riku et al., 2021). Furthermore, the transition of high annual direct healthcare expenditure to potentially greater lifetime costs as a consequence of increased survival of SMA Type 1 patients highlights the dynamic economic environment that requires constant reassessment of treatment cost-effectiveness (Skedgel, 2021).

11. FUTURE DIRECTIONS AND UNMET NEEDS

Despite the great advances in the field of the treatment of SMA, there are a few critical areas which should be studied further in order to optimize the treatment strategies and respond to the challenges. This involves an understanding of the full range of cognitive and neurodevelopment outcomes among patients receiving novel therapies, especially in the light of the fact that these treatments may change the phenotypic expression of the disease (Steffens et al., 2024). In addition, integration of neurodevelopmental screening with comprehensive care models is required to proactively identify and treat potential neurodevelopmental differences in treated SMA populations (Balaji et al., 2025). For instance, there is a significant cumulative frequency of neurodevelopmental disorders, including autism spectrum disorder, in treated SMA patients ranging from 9% to 60% in different studies and there is a great need for thorough investigation into these aspects of this emerging disease (Coratti et al., 2025). Moreover, more research is needed to define the particular mechanisms that support these observations, taking into account such possible confounding factors as genetic modifiers or off-target effects of the therapeutic agents. Furthermore, considering the number of patients are treated with multiple different therapies, the question of which treatment regimens work best remains an area of investigation (Leon-Atlantique et al., 2022).

Ongoing clinical research is also focused on addressing the consequences of SMN loss by therapeutic

agents which are currently in development or already approved for some of the other neuromuscular diseases (Wiedmann & Cairns, 2023). These include therapies that would target muscle strength and functioning, such as activin receptor type IIB inhibitors, and those that would improve the health and survival of neurons. The process of economic evaluation of these emerging therapies will require robust longitudinal cost data, which remains a major gap in the evidence base (Landfeldt et al., 2021). Filling this gap is important for health technology assessment bodies that want to accurately assess the long-term cost-effectiveness and budgetary impact of these innovative treatments, particularly in resource-constrained healthcare systems (Elshahawy et al., 2025; Sutherland et al., 2021). A complete knowledge of the cognitive functioning and brain involvement of individuals with SMA is also important for personalized management of the patient and to identify the appropriate measures for assessment (Giannotta et al., 2024; Masson et al., 2021).

Since a range of individual therapeutic approaches are currently present or under development, including SMN-enhancing agents, splicing modifiers, and gene therapies, the research into the best combination regimens has significant potential in terms of providing synergistic effect and additional improvement of disease progression (Osseni et al., 2025). The latter may result in the possibility of higher clinical outcomes because more pathophysiological pathways would be addressed. This multi-modal treatment protocol is intended to overcome the short-coming of monotherapies which may allow a more comprehensive salvage of the complex neurological and neuromuscular impairment of SMA. Nonetheless, the complicated interaction of various therapeutic systems and their long-term effectiveness and safety profiles implies that combination therapeutic strategies require a well-thought-out set of clinical trials to identify the most effective dosage, order, and patient selection criteria. The excellent recruitment requirements to these investigational drugs highlight the current growth of the clinical trial environment in SMA and the necessity of coordinated research activities (Sarr et al., 2026).

12.CONCLUSION

The management of spinal muscular atrophy has undergone a profound transformation from a predominantly palliative approach to a disease-modifying paradigm that targets the underlying genetic cause, with therapies such as nusinersen, risdiplam, and onasemnogene abeparvovec significantly improving survival, motor function, and quality of life. Early diagnosis and timely intervention, particularly through newborn screening, are critical for achieving optimal outcomes by preventing irreversible motor neuron loss, while the growing role of clinical pharmacists and multidisciplinary care teams supports individualized treatment selection and long-term monitoring. Despite these advancements, several challenges persist, including high treatment costs, limited long-term safety data, variability in therapeutic response, and incomplete disease reversal. Moreover, the development of SMN-independent therapies and effective combination strategies remains an important focus for future research. Overall, although current treatments have redefined SMA as a manageable chronic condition rather than a fatal disorder, continued innovation, improved accessibility, and robust long-term evidence are essential to achieving the ultimate goal of a curative approach.

Conflict of Interest

The authors declare they don't have any conflict of interest.

Author contributions

The initial drafts of the manuscript were prepared jointly by the primary author and the corresponding author's supervisor. All co-authors actively contributed to the conceptualization and execution of the study, sharing responsibilities across data collection, synthesis, and the preparation of all tables and graphical assets. Each author conducted critical revisions to strengthen intellectual content, approved the final revised version, and formally granted consent for submission and publication in the journal.

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