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Review

# Pharmacological and gene therapy for spinal muscular atrophy

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## Abstract

Spinal muscular atrophy (SMA) is a rare autosomal recessive neurodegenerative neuromuscular disorder caused by the progressive degeneration and loss of spinal anterior horn motor neurons. The disease is clinically characterized by symmetric proximal muscle weakness and progressive muscle atrophy affecting the limbs and trunk. In recent years, the approval of the antisense oligonucleotide nusinersen, the oral small-molecule splicing modifier risdiplam, and the AAV9-mediated gene replacement therapy onasemnogene abeparvovec has transformed SMA from a fatal disease with limited treatment options into a chronic condition that can be managed long term. This review summarizes the pathogenesis, clinical classification, and diagnostic features of SMA with a particular focus on recent advances in pharmacological and gene therapy. It also discusses the limitations of current therapeutic approaches, including long-term efficacy, safety, and clinical application, and highlights the future prospects of emerging therapeutic strategies. Overall, existing treatments have substantially improved survival and motor function in patients with SMA. Future efforts should focus on expanding

newborn screening and presymptomatic intervention programs,while promoting precision medicine, individualized treatment, and multidisciplinary care to further improve long-term outcomes and quality of life for patients with SMA.

**Keywords:** Spinal muscular atrophy, survival motor neuron 1, survival motor neuron 2, gene therapy, pharmacological therapy

## INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder characterized by the progressive degeneration and loss of anterior horn motor neurons in the spinal cord[1]. An individual develops SMA only when both parents are carriers, resulting in a 25% risk of inheritance. In China, the carrier frequency of pathogenic SMN1 variants is estimated to be approximately 1.2%-2.2%[2], corresponding to nearly 30 million carriers nationwide[3]. In recent years, advances in the understanding of survival motor neuron (SMN) protein function, the compensatory role of survival motor neuron 2 (SMN2)[4], and gene therapy technologies have led to revolutionary progress in the treatment of SMA. SMN2 splicing-modifying therapies have substantially delayed disease progression, reduced muscle atrophy and skeletal deformities, and significantly improved patients' survival and quality of life. As multiple SMN2 splicing-modifying therapies have become available in clinical practice[5], each therapeutic strategy exhibits distinct characteristics regarding indications, long-term efficacy, safety, and route of administration[6]. Consequently, how to develop precise and individualized treatment strategies based on patient age, clinical phenotype, and disease stage has become a critical challenge in the clinical management of SMA[7]. This review provides a comprehensive overview of current pharmacological and gene therapy approaches for SMA, focusing on the characteristics and clinical applications of different therapeutic strategies. By integrating current evidence, it aims to provide a reference for precision and individualized therapeutic decision-making in SMA and discusses the future prospects of emerging treatment strategies.

## PATHOGENESIS

SMA is an autosomal recessive motor neuron disease. Approximately 95% of patients with SMA have 5q SMA, which is caused by biallelic pathogenic variants in the SMN1 gene located on chromosome 5q13[8]. Loss of SMN1 function results in a severe deficiency of the SMN protein[9], which is essential for the survival and function of motor

neurons. As a core component of the small nuclear ribonucleoprotein (snRNP) complex, the SMN protein plays a critical role in the assembly of spliceosomes, thereby ensuring accurate pre-mRNA splicing[10,11]. SMN deficiency disrupts the splicing of numerous pre-mRNAs, ultimately leading to degeneration and loss of anterior horn motor neurons in the spinal cord[12,13].

Humans possess a highly homologous paralog SMN2, which differs from SMN1 by only a few nucleotides. A critical nucleotide substitution in SMN2 alters pre-mRNA splicing by promoting exclusion of exon 7[14], resulting in the production of only approximately 10% full-length functional SMN protein, with the remaining transcripts encoding unstable truncated proteins[8,15]. Consequently, the SMN2 copy number is inversely correlated with disease severity, a higher copy number leads to increased production of functional SMN protein and is generally associated with a milder clinical phenotype. Therefore, SMN2 is regarded as the most important disease-modifying gene influencing the severity of 5q SMA[5,16].

Approximately 5% of SMA cases are caused by pathogenic variants in genes other than SMN1 and are collectively classified as non-5q SMA, a group of rare genetically heterogeneous disorders[17]. Among these, mutations in the IGHMBP2 gene cause SMA with respiratory distress type 1. The IGHMBP2 gene encodes an RNA helicase involved in RNA metabolism, and its dysfunction leads to progressive motor neuron degeneration, clinically characterized by distal muscle weakness and severe respiratory distress resulting from diaphragmatic paralysis[18].Another subgroup includes SMA with lower extremity predominance, which is caused by mutations in DYNC1H1 or BICD2. Both genes encode proteins involved in intracellular vesicular transport and axonal cargo trafficking. Their disruption impairs neuronal transport and synaptic function, resulting predominantly in proximal lower-limb weakness[19].In addition, pathogenic variants in UBA1 cause X-linked infantile SMA. UBA1 encodes the ubiquitin-activating enzyme, which is a key component of the ubiquitin-proteasome system responsible for protein degradation. Dysfunction of this pathway leads to the accumulation of misfolded or toxic proteins, contributing to motor neuron degeneration[20]. Other rare forms of non-5q SMA have also been associated with pathogenic variants in genes, such as TRPV4 and ASAH1, further highlighting the marked genetic heterogeneity of this group of disorders [Figure 1].

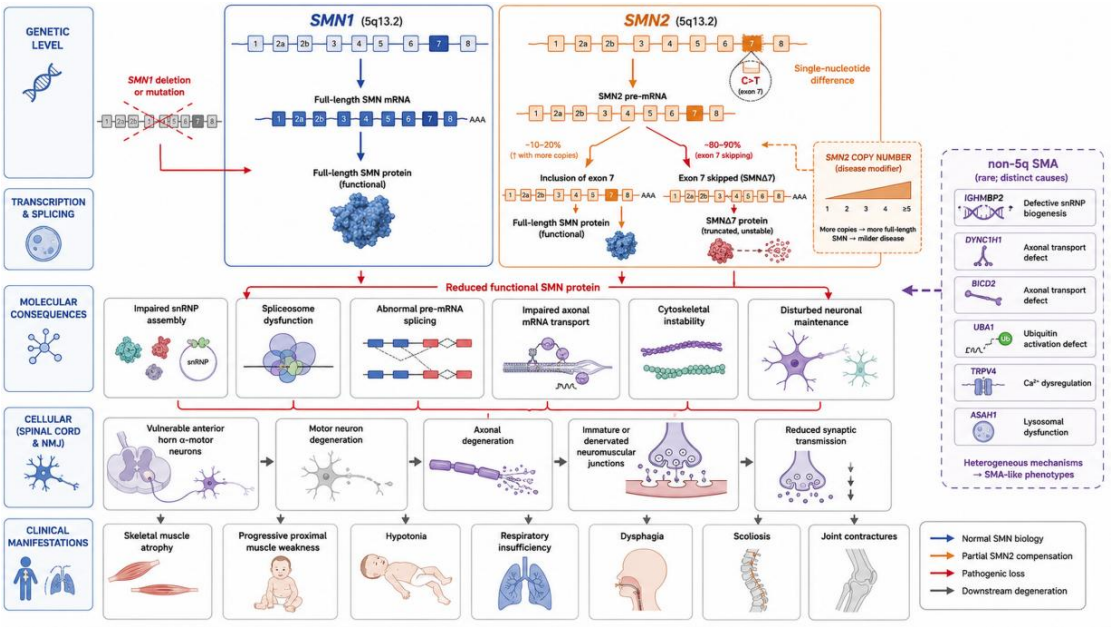


**Figure 1.** Molecular pathogenesis of SMA from SMN gene defects to motor neuron degeneration.

This schematic illustrates the molecular pathogenesis of SMA. In 5q SMA, SMN1 deletion or mutation reduces functional SMN protein, while SMN2 produces only limited full-length SMN because of exon 7 skipping, with SMN2 copy number partially modifying disease severity. SMN deficiency disrupts RNA splicing and neuronal maintenance, leading to motor neuron degeneration, neuromuscular junction dysfunction, muscle atrophy, and the characteristic clinical manifestations of SMA. Rare non-5q SMA results from pathogenic variants in genes such as IGHMBP2, DYNC1H1, BICD2, UBA1, TRPV4, and ASAH1.

## Clinical manifestations and classification

SMA is a hereditary neuromuscular disorder characterized by the progressive degeneration and loss of α-motor neurons in the anterior horn of the spinal cord[1]. The disease typically presents with progressive, symmetrical proximal muscle weakness, muscle atrophy, hypotonia, and diminished or absent deep tendon reflexes[21]. Additional manifestations may include tongue fasciculations, dysphagia, respiratory muscle weakness, scoliosis, and joint contractures, whereas sensory and cognitive functions are generally preserved[22].

Approximately 95% of patients have 5q SMA; therefore, current clinical classification

and therapeutic strategies are primarily based on this subtype. Traditionally, 5q SMA is classified into five clinical types according to the age at symptom onset and the highest motor milestone achieved[23][Figure 2].

(1)Type 0 (prenatal SMA). Symptoms begin during the fetal period, and affected infants present at birth with profound muscle weakness and respiratory failure. This is the most severe form of SMA, with most untreated patients dying of respiratory failure within the first 6 months of life. Patients typically carry zero or one copy of SMN2.

(2)Type I (infantile-onset SMA). Symptom onset occurs before 6 months of age. Patients are unable to achieve independent sitting and typically present with severe hypotonia ("floppy infant"syndrome), feeding and swallowing difficulties, tongue fasciculations, and respiratory insufficiency resulting from intercostal muscle weakness. Without treatment, most patients die or require permanent ventilatory support before 2 years of age. Most patients have one or two copies of SMN2.

(3)Type II (intermediate SMA). Onset occurs between 6 and 18 months of age. Patients are able to sit independently but never achieve independent ambulation. Progressive scoliosis and joint contractures commonly develop during the disease course. Disease progression is relatively slow, and approximately 70% of untreated patients survive beyond 25 years of age. Most patients possess two or three copies of SMN2.

(4)Type III (juvenile-onset SMA). Symptoms develop after 18 months of age. Patients initially achieve independent ambulation but may gradually lose walking ability over time. Disease progression is generally slow, and life expectancy is usually normal or only minimally reduced. Most patients carry three or four copies of SMN2.

(5)Type IV (adult-onset SMA). Symptoms begin during adulthood and are typically limited to mild-to-moderate proximal muscle weakness. This is the mildest clinical phenotype associated with a normal life expectancy. Patients usually have four or more copies of SMN2.

With the widespread use of SMN2 splicing-modifying therapy, the traditional classification system based solely on age at onset and motor milestones no longer

adequately reflects the clinical status of patients[24,25]. Recent international consensus recommendations advocate a functional classification approach that incorporates motor performance, respiratory support requirements, swallowing and nutritional status, treatment response, and SMN2 copy number to enable dynamic disease assessment, guide individualized treatment selection, and optimize long-term follow-up[26].

**Diagnosis**

The Expert Consensus on Newborn Screening (NBS) for SMA (2023) recommends carrier screening for individuals planning pregnancy or during early pregnancy, as well as those with a family history[27]. Currently, genetic testing is the cornerstone for the definitive diagnosis of SMA [Figure 2].

Because more than 95% of patients with SMA harbor a homozygous deletion of exon 7 in SMN1, current screening strategies primarily target this well-established genetic marker[28]. Real-time quantitative polymerase chain reaction (qPCR) is the most widely used screening method and enables rapid and accurate detection of SMN1 exon 7 deletion using either dried blood spot (DBS) samples obtained from neonatal heel-prick blood or peripheral venous blood samples from individuals undergoing testing[29]. Individuals with positive screening results should be recalled for confirmatory testing, which is typically performed using multiplex ligation-dependent probe amplification (MLPA) to determine the copy numbers of both SMN1 and SMN2 [30]. For patients with a high clinical suspicion of SMA but without homozygous SMN1 deletion detected by qPCR or MLPA, further SMN1 gene sequencing is recommended to identify pathogenic sequence variants. In addition, the copy number of SMN2 should be reported simultaneously. Although SMN2 copy number is not used to establish the diagnosis of SMA, it provides important information for assessing disease severity, clinical classification, therapeutic decision-making, and prognosis[16]. Evidence has demonstrated that irreversible motor neuron loss begins before the onset of clinical symptoms in SMA. Therefore, screening, definitive diagnosis, and initiation of treatment during the presymptomatic stage are critical for preserving motor neuron function to the greatest extent possible, thereby significantly improving motor development and long-term clinical outcomes[31,32].

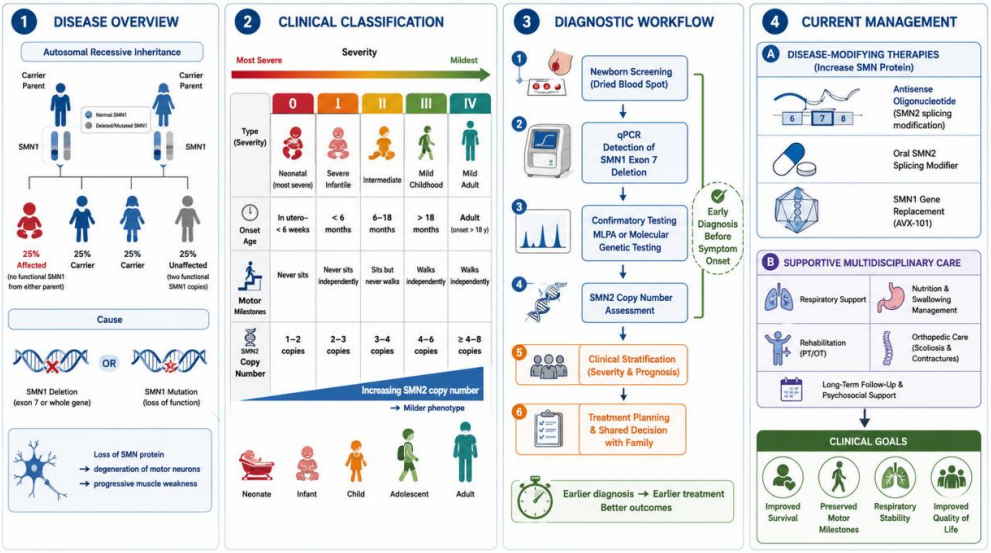


**Figure 2.** Clinical overview of SMA: inheritance, classification, diagnosis, and current management.

This figure summarizes the clinical framework of SMA. SMA is an autosomal recessive neuromuscular disorder caused by SMN1 defects, resulting in reduced SMN protein and progressive motor neuron degeneration. Patients are classified into Types 0-IV according to age at onset and motor function, with higher SMN2 copy number generally associated with milder disease. Diagnosis relies on newborn screening and molecular confirmation, while current management combines SMN-targeted therapies with multidisciplinary supportive care. Early diagnosis and presymptomatic treatment are critical for improving survival, motor function, and quality of life.

## Therapeutic strategies

The aforementioned pathogenesis, clinical manifestations, classification, and diagnostic criteria not only provide the foundation for the comprehensive assessment of SMA but also serve as the basis for therapeutic decision-making. The goals of SMA treatment have evolved from simply prolonging survival to improving motor function, enhancing quality of life, and achieving long-term disease management[33]. Based on their mechanisms of action, current therapeutic strategies can be broadly categorized into SMN2 splicing-modifying therapy, gene therapy, and other emerging therapeutic approaches. Among these, pharmacological therapy, particularly SMN2 splicing-modifying therapy, remains the most widely used disease-modifying treatments in clinical practice[34]. Gene therapy aims to restore SMN protein expression by delivering a functional SMN1 gene, thereby

targeting the underlying genetic cause of the disease and fundamentally altering its progression[35]. In addition, emerging therapeutic strategies, including neuroprotective and combination therapy, are under active investigation and offer promising opportunities to further enhance therapeutic efficacy[5].

*SMN2 splicing-modifying therapy*

SMN2 splicing-modifying therapies represent the first disease-modifying treatment strategy successfully translated into clinical practice for SMA. By correcting the aberrant splicing of SMN2 pre-mRNA and promoting exon 7 inclusion, these therapies increase the production of full-length SMN protein[36], thereby partially compensating for SMN1 deficiency. Currently approved SMN2 splicing modifiers include the antisense oligonucleotide nusinersen and the orally administered small-molecule splicing modifier risdiplam. Although both therapies share the common goal of enhancing SMN protein expression, they differ substantially in their molecular mechanisms, routes of administration, tissue distribution, and clinical characteristics[37][Figure 3].

Nusinersen remains one of the most important SMN2 splicing-modifying therapy currently available. It is an ASO designed to bind to the intronic splicing silencer N1 (ISS-N1) located within intron 7 of SMN2 pre-mRNA[38,39]. By blocking this splicing silencer, nusinersen promotes inclusion of exon 7 in the mature SMN2 transcript, thereby increasing the production of full-length functional SMN protein and partially compensating for the loss of SMN1 function[40]. Because ASOs do not readily cross the blood-brain barrier and the primary pathological targets of SMA are the anterior horn motor neurons of the spinal cord, nusinersen is administered by intrathecal injection to achieve adequate drug delivery to the central nervous system (CNS)[41]. Clinical studies have consistently demonstrated that therapeutic efficacy is highly dependent on the timing of treatment initiation, with earlier intervention resulting in greater preservation of motor neurons and superior functional outcomes. Accordingly, presymptomatic or early treatment has been shown to markedly improve survival and motor development in infants with SMA[42].

Nusinersen has now been approved in numerous countries and is widely used across different subtypes of 5q SMA[43]. The pivotal ENDEAR and CHERISH trials demonstrated that nusinersen significantly improved motor milestone achievement and

event-free survival in patients with infantile- and later-onset SMA. Furthermore, long-term follow-up from the NURTURE study showed that most presymptomatic infants treated before symptom onset achieved major motor milestones, including independent sitting, standing, and even walking, highlighting the critical importance of early intervention[44]. Despite these substantial clinical benefits, nusinersen has several limitations. It primarily improves the function of surviving motor neurons but cannot regenerate neurons that have already been lost, and its therapeutic effects on peripheral tissues remain limited[45]. In addition, repeated intrathecal administration may be technically challenging, particularly in infants and patients with severe scoliosis or complex spinal deformities[46].

Risdiplam is an orally administered SMN2 splicing modifier and a small-molecule RNA splicing modulator approved for the treatment of SMA[47]. Unlike ASO-based therapy, risdiplam exhibits favorable tissue distribution following oral administration, readily enters systemic circulation, and is widely distributed throughout both the CNS and peripheral tissues[48]. In SMNΔ7 mice, treatment with 1 mg/kg/day resulted in approximately 206% and 210% increases in SMN protein expression in the brain and skeletal muscle, respectively, providing therapeutic benefits for both central motor neurons and peripheral pathological abnormalities. This strategy represents a promising approach owing to its noninvasive delivery, systemic distribution, and potential advantages in clinical applicability.

Although both risdiplam and nusinersen increase the production of full-length SMN protein by modulating SMN2 pre-mRNA splicing, they differ substantially in their molecular mechanisms and binding characteristics[37]. Risdiplam acts through a dual-binding mechanism by interacting with two distinct sites on SMN2 pre-mRNA[49]. Binding at the 5′ splice site stabilizes its RNA structure and enhances recognition by U1 small nuclear ribonucleoprotein (U1 snRNP), thereby facilitating spliceosome assembly. In addition, binding to an exonic splicing enhancer within exon 7 is thought to displace inhibitory splicing factors, further promoting exon 7 inclusion and increasing the production of full-length SMN protein.

In summary, SMN2 splicing-modifying therapies enhance the expression of functional SMN protein and have significantly improved survival outcomes and motor function in

patients with SMA, representing a major transition from supportive care to disease-modifying treatment. Nusinersen and risdiplam represent two distinct SMN2-targeted therapeutic approaches, namely antisense oligonucleotide-mediated splicing modulation and small-molecule splicing modification, respectively, and have become the most widely used disease-modifying therapies in clinical practice.

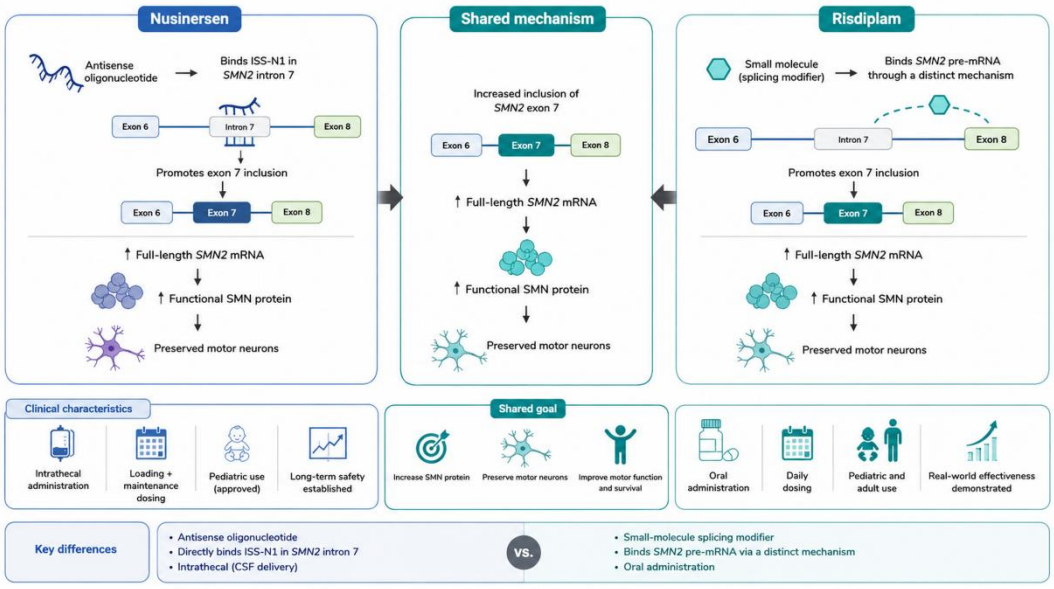


**Figure 3.** Mechanisms and clinical characteristics of SMN2 splicing-modifying therapies for spinal muscular atrophy.

Nusinersen and risdiplam both increase functional SMN protein by promoting exon 7 inclusion in SMN2 pre-mRNA. Nusinersen is an intrathecally administered antisense oligonucleotide that blocks the intronic splicing silencer N1 and mainly acts within the central nervous system. Risdiplam is an oral small-molecule splicing modifier with broader distribution in both central and peripheral tissues. Both improve motor function and survival, but differ mainly in mechanism, administration route, tissue exposure, and treatment burden.

## Gene therapy

SMN2 splicing-modifying therapies require long-term continuous administration and primarily exert effects on surviving motor neurons, making them unable to reverse established neuronal loss. Moreover, differences in drug distribution, administration routes, and disease stages among patients impose limitations on their long-term efficacy and individualized application[45]. Therefore, gene therapy strategies targeting the

underlying genetic defect of SMA have emerged as a major research focus, aiming to restore SMN gene function and achieve more durable and effective disease intervention[50][Figure 4].

*SMN1 gene replacement therapy*

Onasemnogene abeparvovec is a gene replacement therapy designed to address the underlying genetic cause of SMA. It utilizes an adeno-associated virus serotype 9 (AAV9) vector to deliver a functional copy of SMN1 into motor neurons[51]. Following transduction, the introduced SMN1 gene enables sustained expression of functional SMN protein, thereby restoring SMN protein levels, preserving motor neuron survival and function, and fundamentally modifying the disease course[52]. Clinical studies have demonstrated substantial therapeutic benefits, particularly when treatment is initiated before symptom onset or during the early symptomatic stage. A study enrolled 15 infants with SMA1 who had confirmed genetic diagnosis and presented with symptoms. All treated infants survived to ≥ 20 months of age without requiring permanent ventilation, demonstrating a significant improvement in event-free survival rates[53].

Overall, onasemnogene abeparvovec is generally well tolerated; however, adverse events associated with the AAV9 vector require careful monitoring. Because AAV9 exhibits predominant hepatic tropism, hepatotoxicity is the most important safety concern[54]. The U.S. Food and Drug Administration (FDA) has issued a boxed warning regarding the risks of acute serious liver injury and acute liver failure, including fatal cases. Other reported adverse events include thrombocytopenia, elevated cardiac troponin levels, pyrexia, and vomiting. Therefore, comprehensive pretreatment evaluation, particularly assessment of liver function, is recommended, and patients should undergo regular laboratory monitoring for at least three months following infusion[55].

Although current AAV-mediated gene replacement therapies have demonstrated substantial clinical efficacy, their widespread application remains limited by the high vector doses required, the associated risk of hepatotoxicity, and considerable treatment costs[51]. These challenges have driven the development of next-generation AAV vectors aimed at maintaining or enhancing therapeutic efficacy, while reducing vector dosage, improving safety, and expanding treatment eligibility to a broader patient population.

GC101 is a novel AAV-mediated SMN1 gene therapy independently developed in China. It employs codon-optimized SMN1 cDNA (co-SMN1) driven by a cytomegalovirus enhancer/chicken β-actin promoter. GC101 is delivered by a fixed low-dose intrathecal injection directly into the cerebrospinal fluid. This administration strategy minimizes hepatic exposure, enhances targeting of spinal motor neurons, and extends the potential therapeutic window to older and heavier patients[56]. Clinical studies have demonstrated that GC101 is both safe and effective in infants with type I SMA, providing preliminary evidence supporting the feasibility of intrathecal AAV-mediated gene therapy in this population. In a subsequent study involving patients with type II and III SMA across a broader age range, a single intrathecal administration resulted in improved or stabilized motor function over a 52-week follow-up period without treatment-related serious adverse events[57]. Notably, some patients regained advanced motor abilities, including jumping, suggesting sustained functional benefits.

Beyond GC101, several next-generation AAV vectors are currently under development. EXG001-307 uses a human synapsin promoter to achieve neuron-selective transgene expression. Following intrathecal or intracerebroventricular administration, it achieves efficient CNS transduction, while minimizing peripheral exposure. In SMN7 mouse models, EXG001-307 significantly prolonged survival and has progressed to an investigator-initiated clinical trial, making it a promising candidate for next-generation precision gene therapy for SMA[58]. Another investigational vector, SKG0201, incorporates optimized promoter and expression cassette designs to achieve preferential SMN1 expression within the CNS at substantially lower vector doses while markedly reducing hepatic transgene expression, thereby offering the potential for improved safety[59].

Despite these advances, next-generation AAV-based gene therapies continue to face several practical challenges. Although intrathecal administration reduces hepatic exposure, pre-existing anti-AAV neutralizing antibodies in the cerebrospinal fluid may still compromise transduction efficiency[60,61]. In addition, the high vector doses required for therapeutic efficacy continue to pose challenges in manufacturing costs and product pricing, while large-scale production and quality control must also meet stringent regulatory standards. Overall, although engineered AAV vectors have demonstrated improvements in safety and durability of transgene expression, their widespread clinical

implementation will require further validation through large-scale studies with long-term follow-up[62].

**Gene editing therapy**

Gene editing therapy differs fundamentally from conventional therapeutic strategies, such as viral vector-mediated gene replacement and RNA splicing modulation, by directly correcting pathogenic variants at the DNA level with the potential to achieve a definitive cure[63]. In recent years, rapid advances in genome-editing technologies have led to significant progress in the application of base editing (BE), prime editing (PE), and CRISPR-Cas9 for the treatment of SMA[63-65].

BE enables precise single-nucleotide substitutions without inducing DNA double-strand breaks, thereby offering high editing efficiency and an improved safety profile. In a mouse model of SMA, AAV9-mediated delivery of a base editor achieved an average SMN2 to SMN1 conversion efficiency of 87%, resulting in marked improvements in motor function and extending median survival from 17 to 111 days[66]. In another study, an optimized TaC9 adenine base editor (ABE) achieved a 45% target conversion rate in induced pluripotent stem cells (iPSCs) derived from patients with SMA, successfully restoring SMN protein expression and improving the resistance of motor neurons to apoptosis[67]. Like BE, PE enables precise genome modification without introducing DNA double-strand breaks. However, unlike BE, PE is not restricted to single-base substitutions, but directly rewrites target DNA sequences through a “search-and-replace” mechanism, allowing more versatile and complex genetic modifications. Using this strategy, investigators successfully deleted the intronic splicing silencer ISS-N1 within the SMN2 gene in patient-derived iPSCs, thereby restoring the expression of full-length SMN protein[64].

To maximize therapeutic efficacy before irreversible neuronal loss occur, prenatal gene editing has also emerged as a promising strategy. In a fetal mouse model, lipid nanoparticles (LNPs) were used to deliver base editor mRNA into the developing nervous system, achieving efficient in vivo genome editing during fetal development. Compared with postnatal intervention, prenatal gene editing produced greater improvements in survival and disease phenotype, suggesting that intervention during early developmental stages may further enhance therapeutic outcomes[68].

In addition, a study employed the CRISPR/Cpf1 (Cas12a) system in combination with single-stranded oligodeoxynucleotides (ssODNs) to achieve the targeted conversion of SMN2 into SMN1 in induced pluripotent stem cells (iPSCs) derived from patients with SMA, with a conversion efficiency of approximately 11%[69].

Although these studies have demonstrated the potential of gene editing as a curative strategy for SMA, several major challenges remain, including limited delivery efficiency, the risk of off-target mutations, and uncertain long-term safety[70]. First, the delivery efficiency observed in humans is substantially lower than that achieved in mouse models, particularly with respect to achieving widespread and uniform transduction throughout the central nervous system[62,71]. Second, although prenatal gene editing offers a unique therapeutic window before irreversible motor neuron degeneration occurs, the fetal immune system is still immature, and the long-term tolerance to gene-editing products as well as the potential risk of autoimmune responses remain unclear[62]. Overall, considerable obstacles must be overcome before this technology can be translated into clinical practice, with current efforts primarily focused on improving delivery strategies and enhancing genome-editing precision.

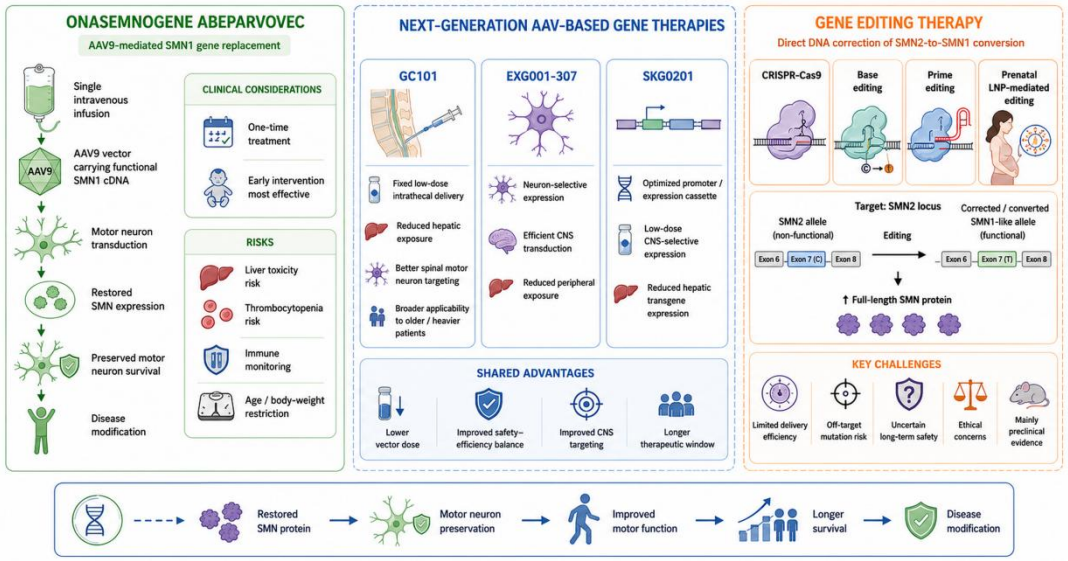


**Figure 4.** Gene replacement, next-generation AAV-based gene delivery, and genome-editing strategies for spinal muscular atrophy.

Onasemnogene abeparvovec is a single-dose AAV9 gene therapy that delivers functional

SMN1 to motor neurons and restores SMN expression. Its use is limited by risks such as hepatotoxicity, thrombocytopenia, immune responses, and age- or weight-based eligibility. Newer AAV therapies aim to improve safety through CNS-targeted delivery, optimized expression systems, and lower vector doses. Genome-editing strategies may provide durable correction of SMN1 or SMN2 defects, but most remain experimental because of delivery challenges, off-target effects, uncertain long-term safety, and ethical concerns.

**Emerging therapeutic strategies**

Gene therapies have introduced an etiological treatment strategy for SMA that is fundamentally distinct from conventional pharmacological therapies and has substantially transformed the therapeutic landscape of the disease. However, challenges related to vector delivery efficiency, immune responses, long-term transgene expression, and clinical accessibility remain unresolved[72]. Consequently, gene replacement alone may not fully address the therapeutic needs of all patients[4]. Therefore, emerging therapeutic approaches based on complementary mechanisms, including neuroprotective and combination therapies, are being actively investigated to further expand the therapeutic potential of SMA and improve long-term clinical outcomes[73][Figure 5].

*Neuroprotective and regenerative therapy*

Neuroprotective and regenerative therapy have emerged as an important direction in SMA research. Unlike SMN-targeted therapy, these SMN-independent approaches aim to preserve surviving motor neurons, promote neuronal repair, and restore neuromuscular connectivity, thereby improving clinical outcomes. As increasing evidence suggests that restoration of SMN protein alone cannot fully reverse established neuronal damage, strategies targeting downstream pathogenic mechanisms are considered promising complementary therapeutic approaches[74,75].

Neuroprotective therapy primarily target signaling pathways involved in motor neuron degeneration. SMN deficiency has been shown to aberrantly activate the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway, thereby contributing to motor neuron injury. The selective p38 MAPK inhibitor MW150 readily crosses the blood-brain barrier and has demonstrated SMN-independent neuroprotective effects in SMA mouse models, resulting in improved motor function. Furthermore, when combined with SMN-

inducing therapy, MW150 promoted synaptic remodeling within spinal sensorimotor circuits, suggesting its potential as an adjunctive therapeutic strategy[76]. Another neuroprotective agent, olesoxime, exerts its effects by stabilizing the outer mitochondrial membrane and inhibiting mitochondrial permeability transition pore opening. Although a phase II clinical trial demonstrated a slower decline in motor function, the primary efficacy endpoint was not met[77,78]. Moreover, long-term follow-up failed to demonstrate sustained stabilization of motor function, ultimately leading to the discontinuation of its clinical development.

In addition to neuroprotection, enhancing skeletal muscle function has become another important SMN-independent therapeutic strategy. Apitegromab, a fully human monoclonal antibody targeting myostatin, promotes muscle growth by inhibiting the negative regulatory effects of myostatin on skeletal muscle development[79]. In the phase II TOPAZ trial, apitegromab demonstrated favorable safety and tolerability in patients with type II and III SMA and provided additional improvements in motor function in patients who had already received nusinersen therapy for more than two years. Subsequently, the phase III SAPPHIRE trial was completed to further evaluate its efficacy in a larger patient population, supporting the potential of muscle-targeted therapy as an important adjunct to SMN2 splicing-modifying therapy[80].

In addition, drug repurposing has emerged as an attractive strategy because of its shorter development timeline and lower cost. The classical antipsychotic haloperidol has been shown to increase SMN protein expression, reduce motor neuron loss, attenuate neuroinflammation, and improve neuromuscular junction integrity in SMA mouse models[81]. Similarly, 10H-phenothiazine, which has previously demonstrated neuroprotective effects in models of Parkinson's disease and Alzheimer's disease, has also shown significant neuroprotective efficacy in both cellular and animal models of SMA, providing further evidence for the potential repositioning of approved drugs in SMA therapy[82].

However, the molecular targets and mechanisms of action of most candidate neuroprotective and regenerative therapy have not yet been fully validated in human SMA. Moreover, the rapid therapeutic benefits observed in animal models have proven difficult to translate into sustained clinical improvements in chronic neurodegenerative disease[78].

Muscle-targeted approaches may provide supportive benefits but cannot address the underlying loss of motor neuron innervation. Overall, the therapeutic value of neuroprotection as a standalone strategy appears to be limited, and substantial preclinical and clinical validation will be required before these approaches can be successfully translated into clinical practice.

*Combination therapeutic strategies*

With the widespread adoption of SMN2 splicing-modifying therapy, combination therapy has emerged as an important area of investigation in SMA[73]. Among currently approved SMN2 splicing-modifying therapies, nusinersen and risdiplam target SMN2 pre-mRNA splicing but act through distinct and complementary molecular mechanisms. A recent study demonstrated that compared with nusinersen monotherapy, combination treatment with nusinersen and risdiplam in children with type II SMA produced greater improvements in motor function, pulmonary function, and quality of life without significantly increasing adverse events. Moreover, the combination appeared to provide superior neuroprotective and muscle-preserving effects, supporting the potential clinical benefit of dual SMN-targeted therapy[41]. Another strategy involves the sequential use of risdiplam following onasemnogene abeparvovec gene replacement therapy, particularly in patients who exhibit suboptimal therapeutic responses or secondary functional deterioration after gene therapy. In a multicenter case series involving five children who experienced progressive decline in motor or respiratory function after treatment with onasemnogene abeparvovec, four patients demonstrated improvements in motor, swallowing, and respiratory function following the addition of risdiplam, whereas the remaining patient achieved clinical stabilization. Importantly, the combination regimen was generally well tolerated, suggesting that sequential treatment may provide additional therapeutic benefit in selected patients[83].

Beyond combinations of SMN-targeted therapy, increasing attention has been directed toward integrating SMN-independent therapy with SMN2 splicing-modifying therapy. Histone deacetylase 6 (HDAC6) inhibitors enhance microtubule acetylation, thereby promoting muscle differentiation and improving neuromuscular function. In a severe SMA mouse model, the HDAC6 inhibitor TubA, when administered in combination with ASO, further enhanced muscle strength, improved histopathological outcomes, and prolonged survival compared with ASO treatment alone. These findings provide

important preclinical evidence supporting the combination of SMN-targeted therapy with neuroprotective and muscle-directed interventions[84]. However, the current evidence is derived primarily from small-scale or retrospective studies, with a lack of support from large randomized controlled trials[85]. Therefore, rigorously designed clinical trials are required to establish the net clinical benefit and risk-benefit profile of these interventions before their widespread implementation, as well as to define precise criteria for patient selection.

In summary, the therapeutic landscape of SMA has evolved into a comprehensive treatment paradigm centered on SMN2 splicing-modifying therapy, advanced by gene therapy, and complemented by emerging therapeutic approaches. Moving forward, the rational integration of different treatment strategies and the implementation of precision, individualized therapeutic approaches are expected to further improve long-term clinical outcomes and optimize patient care.

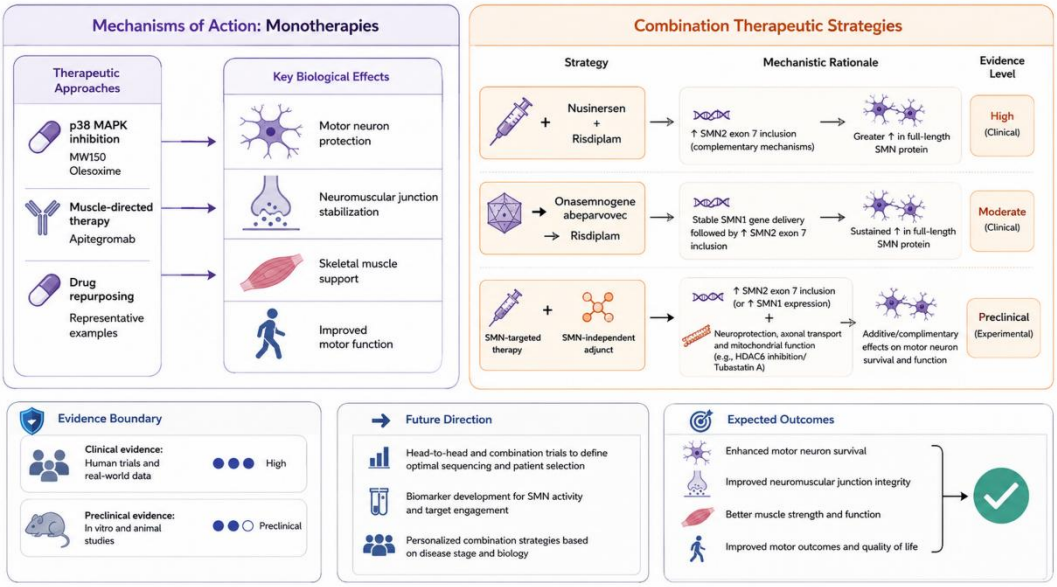


**Figure 5.** Emerging SMN-independent and combination therapeutic strategies for spinal muscular atrophy.

SMN-independent therapies target persistent neuronal, neuromuscular-junction, and muscle dysfunction despite SMN restoration. Examples include the p38 MAPK inhibitor MW150, the mitochondrial agent olesoxime, the myostatin inhibitor apitegromab, and repurposed neuroprotective drugs. Combination strategies pair SMN-targeted treatments with each other or with downstream neuronal and muscle-directed therapies. However,

supporting evidence remains limited, and larger randomized trials are needed to define efficacy and patient selection.

## CHALLENGES AND FUTURE PERSPECTIVES

Although SMN2 splicing-modifying therapies have markedly improved survival and motor outcomes in patients with SMA, current treatments are unable to reverse irreversible motor neuron loss that has already occurred. Furthermore, substantial inter individual variability in treatment response persists, and many patients continue to experience residual functional impairment[7]. In addition, currently available therapeutic strategies differ considerably in their indications, long-term efficacy, and safety profiles. Robust evidence regarding optimal treatment selection, combination therapy, and long-term disease management remains limited[85]. Meanwhile, gene replacement, genome-editing therapy and emerging technologies have demonstrated considerable therapeutic potential; however, their long-term safety, durability of efficacy, and accessibility require further validation in clinical studies[86].

Future advances in SMA management are expected to emphasize earlier intervention, precision medicine, and comprehensive multidisciplinary care. Expanding screening programs and improving screening coverage, together with further exploration of prenatal and presymptomatic interventions[87], will help maximize the opportunity for treatment before irreversible neuronal injury occurs. At the same time, the development of precision medicine should be promoted through the integration of multidimensional clinical and molecular information, including SMN2 copy number, clinical phenotype, and functional status, to facilitate risk stratification, individualized treatment selection, and dynamic disease monitoring[88]. Finally, as life expectancy continues to improve, multidisciplinary management involving neurologists, pulmonologists, rehabilitation specialists, nutritionists, and other healthcare professionals will become increasingly important for optimizing long-term outcomes and improving quality of life in patients with SMA[89].

## CONCLUSION

In recent years, advances in the understanding of SMA pathogenesis have shifted therapeutic strategies from supportive care toward disease-modifying treatments centered on restoring SMN protein expression. SMN2 splicing-modifying therapies and SMN1 gene replacement therapy have significantly improved patient survival and motor

function, while emerging approaches, including gene editing, neuroprotective strategies, and combination therapies, have shown promising potential. However, current treatments remain limited by factors such as treatment timing, safety concerns, and interindividual variability. Future efforts should integrate newborn screening, precision stratification, and multimodal therapeutic approaches to promote individualized management and long-term clinical benefits for patients with SMA.

## DECLARATIONS

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**Conflicts of Interest**

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this study.

**Ethical approval and consent to participate**

Not applicable.

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Not applicable.

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**REFERENCE**

[1] Rodriguez K, Karamitopoulos M. Spinal Muscular Atrophy (SMA)[J]. *Operative Techniques in Orthopaedics*, 2025, 35(3): 1-6.[DOI:10.1016/j.oto.2026.101213]

[2] Sun Y, Ma S, Xiao J, et al. Preconception or prenatal acceptance of SMN1 gene carrier screening and carrier rate of spinal muscular atrophy: a retrospective study in 18,818 reproductive age women in Wuhan area of China[J]. *J Assist Reprod Genet*, 2024, 41(1): 127-33.[PMID: 37991656 PMCID: PMC10789693 DOI: 10.1007/s10815-023-02991-w]

[3] Li C, Geng Y, Zhu X, et al. The prevalence of spinal muscular atrophy carrier in China[J]. *Medicine*, 2020, 99(5): 1-8.[PMID: 32000428 PMCID: PMC7004774 DOI: 10.1097/MD.0000000000018975]

[4] Haque U S, Yokota T. Recent Progress in Gene-Targeting Therapies for Spinal Muscular Atrophy: Promises and Challenges[J]. *Genes (Basel)*, 2024, 15(8): 1-26.[PMID: 39202360 PMCID: PMC11353366 DOI: 10.3390/genes15080999]

[5] Weng W-C, Lee W-T, Chien Y-H, et al. Updates of spinal muscular atrophy in advanced therapies[J]. *Journal of the Formosan Medical Association*, 2026, 125: S73-80.[PMID: 41109767 DOI: 10.1016/j.jfma.2025.10.018]

[6] Signoria I, Zwartkruis M M, Geerlofs L, et al. Patient-specific responses to SMN2 splice-modifying treatments in spinal muscular atrophy fibroblasts[J]. *Mol Ther Methods Clin Dev*, 2024, 32(4): 1-18.[PMID: 39655308 PMCID: PMC11626024 DOI: 10.1016/j.omtm.2024.101379]

[7] Mercuri E, Cicala G, Villa M, et al. What did we learn from new treatments in SMA? A narrative review[J]. *Acta Myol*, 2025, 44(1): 28-32.[PMID: 40183438 PMCID: PMC11978431 DOI: 10.36185/2532-1900-1043]

[8] Lorson C L, Hahnen E, Androphy E J, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy[J]. *Proc Natl Acad Sci U S A*, 1999, 96(11): 6307-11.[PMID: 10339583 PMCID: PMC26877 DOI: 10.1073/pnas.96.11.6307]

[9] Mcpheron M A, Felker M V. Clinical perspectives: Treating spinal muscular atrophy[J]. *Mol Ther*, 2024, 32(8): 2489-504.[PMID: 38894541 PMCID: PMC11405177 DOI: 10.1016/j.ymthe.2024.06.020]

[10]Meister G, Hannus S, Plottner O, et al. SMNrp is an essential pre-mRNA splicing factor required for the formation of the mature spliceosome[J]. *EMBO J*, 2001, 20(9): 2304-14.[PMID: 11331595 PMCID: PMC125440 DOI: 10.1093/emboj/20.9.2304]

[11]Liu Q D G. A novel nuclear structure containing the survival of motor neurons protein.[J], 1996, 15(14): 3555-65.[PMID: 8670859 PMCID: PMC451956]

[12]López-Cortés A, Echeverría-Garcés G, Ramos-Medina M J. Molecular Pathogenesis and New Therapeutic Dimensions for Spinal Muscular Atrophy[J]. *Biology*, 2022, 11(6): 1-21.[PMID: 35741415 PMCID: PMC9219894 DOI: 10.3390/biology11060894]

[13]Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene[J]. *Cell*, 1995, 80(1): 155-65.[PMID: 7813012 DOI: 10.1016/0092-8674(95)90460-3]

[14]Battle D J, Kasim M, Yong J, et al. The SMN complex: an assembly machine for RNPs[J]. *Cold Spring Harb Symp Quant Biol*, 2006, 71: 313-20.[PMID: 17381311 DOI: 10.1101/sqb.2006.71.001]

[15]Sivaramakrishnan M, Mccarthy K D, Campagne S, et al. Binding to SMN2 pre-mRNA-protein complex elicits specificity for small molecule splicing modifiers[J]. *Nat Commun*, 2017, 8(1): 1-13.[PMID: 29133793 PMCID: PMC5684323 DOI: 10.1038/s41467-017-01559-4]

[16]Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases[J]. *Neuromuscul Disord*, 2018, 28(3): 208-15.[PMID: 29433793 DOI: 10.1016/j.nmd.2018.01.003]

[17]Pinto W, Souza P V S, Badia B M L, et al. Adult-onset non-5q proximal spinal muscular atrophy: a comprehensive review[J]. *Arq Neuropsiquiatr*, 2021, 79(10): 912-23.[PMID: 34706022 DOI: 10.1590/0004-282X-ANP-2020-0429]

[18]Vosatkova A, Renczesova B, Martinka I, et al. 530PNon-5q spinal muscular atrophy (SMA) previously followed-up as 5q SMA IIIa - case report[J]. *Neuromuscular Disorders*, 2025, 53(S): 44-5.[https://doi.org/10.1016/j.nmd.2025.105619]

[19]Peeters K, Litvinenko I, Asselbergh B, et al. Molecular Defects in the Motor Adaptor BICD2 Cause Proximal Spinal Muscular Atrophy with Autosomal-Dominant Inheritance[J]. *The American Journal of Human Genetics*, 2013, 92(6): 955-64.[PMID: 23664119 PMCID: PMC3675262 DOI: 10.1016/j.ajhg.2013.04.013]

[20]Balak C D, Hunter J M, Ahearn M E, et al. Functional characterizations of rare UBA1 variants in X-linked Spinal Muscular Atrophy[J]. *F1000Research*, 2017, 6: 1-14.[PMID: 29034082 PMCID: PMC5615770 DOI: 10.12688/f1000research.11878.1]

[21]Pan W, Cao Y Y. Research progress on phenotypic modifier genes in spinal muscular atrophy[J]. *Zhongguo Dang Dai Er Ke Za Zhi*, 2025, 27(2): 229-35.[PMID: 39962788 PMCID: PMC11838024 DOI: 10.7499/j.issn.1008-8830.2410064]

[22]Y W, Cj W. Advances in diagnosis and treatment of spinal muscular atrophy[J]. *Chinese Journal of Medical Frontiers*, 2026, 18(2): 22-9.

[23]Atrophy W G O C P G F S M. Clinical Practice Guidelines for Spinal Muscular Atrophy[J]. *China Journal of Evidence-Based Pediatrics*, 2023, 18(1): 1-12.[PMID: 32128742 DOI: 10.3760/cma.j.issn.1003-9406.2020.03.007]

[24]Varone A, Esposito G, Bitetti I. Spinal muscular atrophy in the era of newborn screening: how the classification could change[J]. *Frontiers in Neurology*, 2025, 16: 1-10.[PMID: 40401019 PMCID: PMC12092217 DOI: 10.3389/fneur.2025.1542396]

[25]Mercuri E, Pera M C, Scoto M, et al. Spinal muscular atrophy - insights and challenges in the treatment era[J]. *Nat Rev Neurol*, 2020, 16(12): 706-15.[PMID: 33057172 DOI: 10.1038/s41582-020-00413-4]

[26]Schroth M K, Deans J, Bharucha Goebel D X, et al. Spinal Muscular Atrophy Update in Best Practices: Recommendations for Treatment Considerations[J]. *Neurol Clin Pract*, 2025, 15(1): 1-13.[PMID: 39399564 PMCID: PMC11464225 DOI: 10.1212/CPJ.0000000000200374]

[27]Expert Group of the Special Fund for Prevention and Control of Neurological and Muscular Diseases E B T N P C O T C R H a a T C B. Expert Consensus on Neonatal Screening for Spinal Muscular Atrophy (2023 Edition)[J]. *Chinese Medical Journal*, 2023, 103(27): 2075-81.[PMID: 37455125 DOI: 10.3760/cma.j.cn112137-20230310-00372]

[28]Chien Y H, Chiang S C, Weng W C, et al. Presymptomatic Diagnosis of Spinal Muscular Atrophy Through Newborn Screening[J]. *J Pediatr*, 2017, 190: 124-9.[PMID: 28711173 DOI: 10.1016/j.jpeds.2017.06.042]

[29]Lee F K, Greene C, Mercer K, et al. CDC's Laboratory Activities to Support Newborn Screening for Spinal Muscular Atrophy[J]. I*nternational Journal of Neonatal Screening*, 2024, 10(3): 1-10.[PMID: 39051407 PMCID: PMC11270301 DOI: 10.3390/ijns10030051]

[30]Wang C-H, Hsu T-R, Liu M-Y, et al. Newborn screening facilitates early theranostics and improved spinal muscular atrophy outcome: five-year real-world evidence from Taiwan[J]. *Orphanet Journal of Rare Diseases*, 2025, 20(1): 1-12.[PMID: 40275389 PMCID: PMC12023543 DOI: 10.1186/s13023-025-03697-1]

[31]Tãtaru E-A, Ouillade M-C, Chan C-H, et al. Incorporating a new disease in the newborn screening programs in Europe: the spinal muscular atrophy case study[J]. *Rare Disease and Orphan Drugs Journal*, 2024, 3(3): 1-10.[DOI: 10.20517/rdodj.2024.08]

[32]Cooper K, Nalbant G, Sutton A, et al. Systematic Review of Presymptomatic Treatment for Spinal Muscular Atrophy[J]. *Int J Neonatal Screen*, 2024, 10(3): 1-31.[PMID: 39189228 PMCID: PMC11348213 DOI: 10.3390/ijns10030056]

[33]Ropars J, Peudenier S, Genot A, et al. Multidisciplinary approach and psychosocial management of spinal muscular atrophy (SMA)[J]. *Arch Pediatr*, 2020, 27(7S): 7S45-49.[PMID: 33357598 DOI: 10.1016/S0929-693X(20)30277-3]

[34]Lakhina Y, Boulis N M, Donsante A. Current and emerging targeted therapies for spinal muscular atrophy[J]. *Expert Rev Neurother*, 2023, 23(12): 1189-99.[PMID: 37843301 DOI: 10.1080/14737175.2023.2268276]

[35]Das S, Mishra A, Palei N N. Emerging therapeutic strategies and clinical management of spinal muscular atrophy[J]. *Discover Neuroscience*, 2026, 21(1): 1-28.[https://doi.org/10.1186/s13064-026-00280-7]

[36]Virata M C A, Abello R M R, Brillante E M B, et al. SMN2 as a therapeutic target in spinal muscular atrophy: advances in gene expression modulation[J]. *Journal of Translational Genetics and Genomics*, 2025, 9(4): 268-85.[DOI: 10.20517/jtgg.2025.56]

[37]Torroba B, Macabuag N, Haisma E M, et al. RNA-based drug discovery for spinal muscular atrophy: a story of small molecules and antisense oligonucleotides[J]. *Expert Opinion on Drug Discovery*, 2022, 18(2): 181-92.[PMID: 36408582 DOI: 10.1080/17460441.2022.2149733]

[38]Hua Y, Vickers T A, Okunola H L, et al. Antisense Masking of an hnRNP A1/A2 Intronic Splicing Silencer Corrects SMN2 Splicing in Transgenic Mice[J]. *The American Journal of Human Genetics*, 2008, 82(4): 834-48.[PMID: 18371932 PMCID: PMC2427210 DOI: 10.1016/j.ajhg.2008.01.014]

[39]Singh N N, Ottesen E W, Singh R N. Nusinersen: the antisense oligonucleotide at the forefront of spinal muscular atrophy treatment[J]. *RNA Biology*, 2026, 23(1): 1-21.[PMID: 42149739 PMCID: PMC13203021 DOI: 10.1080/15476286.2026.2675858]

[40]Hua Y, Sahashi K, Hung G, et al. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model[J]. *Genes Dev*, 2010, 24(15): 1634-44.[PMID: 20624852 PMCID: PMC2912561 DOI: 10.1101/gad.1941310]

[41]Zhen Yuanyuan, Liao Peiyuan, Jing Y, et al. Clinical study of intrathecal injection of nusinersen sodium combined with risdiplam in the treatment of children with spinal muscular atrophy[J]. *China Journal of Clinical Pharmacology*, 2026, 42(10): 1359-64.

[42]Crawford T O, Swoboda K J, De Vivo D C, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of theNURTUREstudy[J]. *Muscle & Nerve*, 2023, 68(2): 157-70.[https://doi.org/10.1002/mus.27853]

[43]Hoy S M. Nusinersen: A Review in 5q Spinal Muscular Atrophy[J]. *CNS Drugs*, 2021, 35(12): 1317-28.[PMID: 34850360 PMCID: PMC8709816 DOI: 10.1007/s40263-021-00878-x]

[44]Finkel R S, Mercuri E, Darras B T, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy[J]. *The New England journal of medicine*, 2017, 377(18): 1723-32.[PMID: 29091570 DOI: 10.1056/NEJMoa1702752]

[45]Wurster C, Petri S. Progress in spinal muscular atrophy research[J]. *Current Opinion in Neurology*, 2022, 35(5): 693-8.[PMID: 35942665 DOI: 10.1097/WCO.0000000000001102]

[46]Talbot K, Tizzano E F. The clinical landscape for SMA in a new therapeutic era[J]. *Gene Therapy*, 2017, 24(9): 529-33.[PMID: 28644430 PMCID: PMC5628264 DOI: 10.1038/gt.2017.52]

[47]Ratni H, Ebeling M, Baird J, et al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA)[J]. *Journal of Medicinal Chemistry*, 2018, 61(15): 6501-17.[PMID: 30044619 DOI: 10.1021/acs.jmedchem.8b00741]

[48]Poirier A, Weetall M, Heinig K, et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs[J]. *Pharmacology Research & Perspectives*, 2018, 6(6): 1-12.[PMID: 30519476 PMCID: PMC6262736 DOI: 10.1002/prp2.447]

[49]Tang Z, Akhter S, Ramprasad A, et al. Recognition of single-stranded nucleic acids by small-molecule splicing modulators[J]. *Nucleic Acids Research*, 2021, 49(14): 7870-83.[PMID: 34283224 PMCID: PMC8373063 DOI: 10.1093/nar/gkab602]

[50]Barkats M. SMA: from gene discovery to gene therapy[J]. *Med Sci (Paris)*, 2020, 36(2): 137-40.[PMID: 32129749 DOI: 10.1051/medsci/2020010]

[51]Pattali R, Mou Y, Li X J. AAV9 Vector: a Novel modality in gene therapy for spinal muscular atrophy[J]. *Gene Ther*, 2019, 26(7-8): 287-95.[PMID: 31243392 DOI: 10.1038/s41434-019-0085-4]

[52]Saraiva J, Nobre R J, Pereira De Almeida L. Gene therapy for the CNS using AAVs: The impact of systemic delivery by AAV9[J]. *J Control Release*, 2016, 241: 94-109.[PMID: 27637390 DOI: 10.1016/j.jconrel.2016.09.011]

[53]Mendell J R, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy[J]. *The New England Journal of Medicine*, 2017, 377(18): 1713-22.[PMID: 29091557 DOI: 10.1056/NEJMoa1706198]

[54]Hoy S M. Onasemnogene Abeparvovec: First Global Approval[J]. *Drugs*, 2019, 79(11): 1255-62.[PMID: 31270752 DOI: 10.1007/s40265-019-01162-5]

[55]Day J W, Finkel R S, Chiriboga C A, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial[J]. *Lancet Neurol*, 2021, 20(4): 284-93.[PMID: 33743238 DOI: 10.1016/S1474-4422(21)00001-6]

[56]Ma X, Zhuang L, Ma W, et al. Treatment of SMA type 1 infants using a single-dose AAV9-mediated gene therapy via intrathecal injection of GC101: An open-label, single-arm study[J]. *Chinese Medical Journal*, 2024, 137(16): 1976-8.[PMID: 39030070 PMCID: PMC11332719 DOI: 10.1097/CM9.0000000000003210]

[57]Ma X-W, Jiang X-Y, Li Z-Q, et al. Single-dose GC101 gene therapy for spinal muscular atrophy types II and III: an open-label single-arm study[J]. *World Journal of Pediatrics*, 2025, 21(9): 935-40.[PMID: 40758201 PMCID: PMC12433340 DOI: 10.1007/s12519-025-00955-x]

[58]Song C, Liu J, Wang Q, et al. Challenging the more-is-better dogma: A precision-optimized AAV gene therapy for SMA[J]. *Molecular Therapy*, 2026, 34(7): 3783-

804.[PMID: 41992613 PMCID: PMC13330066 (available on 2027-07-01) DOI: 10.1016/j.ymthe.2026.04.027]

[59]Yu Y, Qin X, Jing M, et al. Low-dose AAV9-SMN1 with CNS-selective expression delivers efficacy and favorable safety in spinal muscular atrophy[J]. *Molecular Therapy*, 2026, 34(6): 3287-99.[PMID: 41782369 PMCID: PMC13239672 (available on 2027-06-03) DOI: 10.1016/j.ymthe.2026.02.050]

[60]Sakai A, Sugiyama M, Onodera M, et al. Adeno-Associated Virus Gene Therapy for Spinal Muscular Atrophy Induces Hepatotoxicity via Cytokine and Macrophage Activation[J]. *Liver Int*, 2026, 46(8): 1-7.[PMID: 42400303 PMCID: PMC13332412 DOI: 10.1111/liv.70760]

[61]Shirley J L, De Jong Y P, Terhorst C, et al. Immune Responses to Viral Gene Therapy Vectors[J]. *Mol Ther*, 2020, 28(3): 709-22.[PMID: 31968213 PMCID: PMC7054714 DOI: 10.1016/j.ymthe.2020.01.001]

[62]Hatanaka F, Suzuki K, Shojima K, et al. Therapeutic strategy for spinal muscular atrophy by combining gene supplementation and genome editing[J]. *Nature Communications*, 2024, 15(1): 1-14.[PMID: 39048567 PMCID: PMC11269569 DOI: 10.1038/s41467-024-50095-5]

[63]Ponomarev A S, Chulpanova D S, Yanygina L M, et al. Emerging Gene Therapy Approaches in the Management of Spinal Muscular Atrophy (SMA): An Overview of Clinical Trials and Patent Landscape[J]. *Int J Mol Sci*, 2023, 24(18): 1-21.[PMID: 37762045 PMCID: PMC10530942 DOI: 10.3390/ijms241813743]

[64]Zhou M, Tang S, Duan N, et al. Targeted-Deletion of a Tiny Sequence via Prime Editing to Restore SMN Expression[J]. *International Journal of Molecular Sciences*, 2022, 23(14): 1-14.[PMID: 35887289 PMCID: PMC9317564 DOI: 10.3390/ijms23147941]

[65]Alves C R R, Ha L L, Yaworski R, et al. Optimization of base editors for the functional correction of SMN2 as a treatment for spinal muscular atrophy[J]. *Nat Biomed Eng*, 2024, 8(2): 118-31.[PMID: 38057426 PMCID: PMC10922509 DOI: 10.1038/s41551-023-01132-z]

[66]Arbab M, Matuszek Z, Kray K M, et al. Base editing rescue of spinal muscular atrophy in cells and in mice[J]. *Science*, 2023, 380(6642): 1-39.[PMID: 36996170 PMCID: PMC10270003 DOI: 10.1126/science.adg6518]

[67]Chen M, Peng X, Chi Y, et al. Improvement of TaC9-ABE mediated correction of human SMN2 gene[J], 2024, 121(10): 1-10.[PMID: 38923503 DOI: 10.1002/bit.28780]

[68]Carpenter M D, Kus N, Choi R B, et al. Systemic mRNA-LNP administration in fetuses improves survival in a mouse model of spinal muscular atrophy[J]. *Molecular Therapy Methods & Clinical Development*, 2025, 33(4): 1-13.[PMID: 41210168 PMCID: PMC12590276 DOI: 10.1016/j.omtm.2025.101599]

[69]Zhou M, Hu Z, Qiu L, et al. Seamless Genetic Conversion of SMN2 to SMN1 via CRISPR/Cpf1 and Single-Stranded Oligodeoxynucleotides in Spinal Muscular Atrophy Patient-Specific Induced Pluripotent Stem Cells[J]. *Hum Gene Ther*, 2018, 29(11): 1252-63.[PMID: 29598153 DOI: 10.1089/hum.2017.255]

[70]Mengistu G. CRISPR-Cas Systems in Human Disease Therapy: Advances, Clinical Applications, Limitations, and Future Directions[J]. *J Gene Med*, 2026, 28(4): 1-19.[PMID: 41952451 DOI: 10.1002/jgm.70091]

[71]Jeanne M, Chung W K. Opportunities and Challenges of Fetal Gene Therapy[J]. *Prenat Diagn*, 2025, 45(6): 764-71.[PMID: 40325787 DOI: 10.1002/pd.6809]

[72]Khawaja S, Ali R H, Ahmed I, et al. Gene Therapy in Rare Genetic Disorders: Current Progress and Future Perspectives[J]. *Curr Genomics*, 2025, 26(4): 278-89.[PMID: 41235102 PMCID: PMC12606653 DOI: 10.2174/0113892029361490250310041259]

[73]Moultrie F, Chiverton L, Hatami I, et al. Pushing the boundaries: future directions in the management of spinal muscular atrophy[J]. *Trends Mol Med*, 2025, 31(4): 307-318.[PMID: 39794178 DOI: 10.1016/j.molmed.2024.12.006]

[74]Li Y, Zeng H, Wei Y, et al. An Overview of the Therapeutic Strategies for the Treatment of Spinal Muscular Atrophy[J]. *Hum Gene Ther*, 2023, 34(5-6): 180-91.[PMID: 36762938 DOI: 10.1089/hum.2022.189]

[75]Chen T H. New and Developing Therapies in Spinal Muscular Atrophy: From Genotype to Phenotype to Treatment and Where Do We Stand?[J]. *Int J Mol Sci*, 2020, 21(9): 1-20.[PMID: 32392694 PMCID: PMC7246502 DOI: 10.3390/ijms21093297]

[76]Carlini M J, Espinoza-Derout J, Van Alstyne M, et al. Identification of p38 MAPK inhibition as a neuroprotective strategy for combinatorial SMA therapy[J]. *EMBO Molecular Medicine*, 2025, 17(10): 2762-86.[PMID: 40926051 PMCID: PMC12514318 DOI: 10.1038/s44321-025-00303-6]

[77]Bertini E, Dessaud E, Mercuri E, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial[J]. *Lancet Neurol*, 2017, 16(7): 513-22.[PMID: 28460889 DOI: 10.1016/S1474-4422(17)30085-6]

[78]Muntoni F, Bertini E, Comi G, et al. Long-term follow-up of patients with type 2 and non-ambulant type 3 spinal muscular atrophy (SMA) treated with olesoxime in the OLEOS trial[J]. *Neuromuscular Disorders*, 2020, 30(12): 959-69.[PMID: 33246887 DOI: 10.1016/j.nmd.2020.10.008]

[79]Crawford T O, Day J W, De Vivo D C, et al. Long-term efficacy, safety, and patient-reported outcomes of apitegromab in patients with spinal muscular atrophy: results from the 36-month TOPAZ study[J]. *Front Neurol*, 2024, 15: 1-9.[PMID: 39105058 PMCID: PMC11299114 DOI: 10.3389/fneur.2024.1419791]

[80]Crawford T O, Darras B T, Day J W, et al. Safety and Efficacy of Apitegromab in Patients With Spinal Muscular Atrophy Types 2 and 3[J]. *Neurology*, 2024, 102(5): 1-13.[PMID: 38330285 PMCID: PMC11067700 DOI: 10.1212/WNL.0000000000209151]

[81]Menduti G, Perez-Gomez R, Berenger-Currias N, et al. Haloperidol induces neuroprotection and enhances neuromuscular function in both murine and human models of spinal muscular atrophy[J]. *Experimental & Molecular Medicine*, 2026, 58(4): 1216-1229.[PMID: 41974892 PMCID: PMC13144737 DOI: 10.1038/s12276-026-01689-0]

[82]Rasà D M, Stanga S, Santonicola P, et al. 10H-phenothiazine exerts beneficial effects in spinal muscular atrophy in vitro and in vivo models[J]. *Scientific Reports*, 2025, 15(1): 1-11.[PMID: 41402453 PMCID: PMC12756266 DOI: 10.1038/s41598-025-28547-9]

[83]Stoltenburg C, Goldhahn K, Von Moers A, et al. Risdiplam Add-On Therapy Following Onasemnogene Abeparvovec in Children With Spinal Muscular Atrophy and 2 SMN2 Copies: A Multi-Center Case Series[J]. *Muscle & Nerve*, 2026, 73(6): 1164-71.[PMID: 41964328 PMCID: PMC13138358 DOI: 10.1002/mus.70246]

[84]Osseni A, Slika R, Coudert L, et al. Combining SMN2 splicing modifiers with HDAC6 inhibition improves spinal muscular atrophy outcomes[J]. *Brain*, 2026: 1-31.[PMID: 42068140 DOI: 10.1093/brain/awag148]

[85]Bemanalizadeh M, Heidary L, Dakkali M S, et al. Combination therapies in spinal muscular atrophy: a systematic review[J]. *Eur J Pediatr*, 2025, 184(9): 1-13.[PMID: 40879810 DOI: 10.1007/s00431-025-06386-0]

[86]Gopi S, Prethiba S, Chandhru M, et al. Beyond SMN1 mutation: environmental predispositions and epigenetic contributors to phenotypic variability and disease severity in spinal muscular atrophy[J]. *Neuroscience*, 2026, 608: 74-92.[PMID: 42105903 DOI: 10.1016/j.neuroscience.2026.05.008]

[87]Laugel V. Presymptomatic detection of spinal muscular atrophy: Ongoing revolution for a devastating disorder[J]. *Rev Neurol (Paris)*, 2025, 181(9): 909-14.[PMID: 41238319 DOI: 10.1016/j.neurol.2025.08.005]

[88]Corti S, Ottoboni L, Sansone V. Advancing personalized spinal muscular atrophy care: matching the right biomarker to the right patient at the right time[J]. *J Neurol*, 2025, 272(9): 1-22.[PMID: 40892138 PMCID: PMC12405325 DOI: 10.1007/s00415-025-13314-7]

[89]Song W, Ke X. Rehabilitation management for patients with spinal muscular atrophy: a review[J]. *Orphanet Journal of Rare Diseases*, 2025, 20(1): 1-11.[PMID: 40640932 PMCID: PMC12243183 DOI: 10.1186/s13023-025-03888-w]