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Review

Pushing the boundaries: future directions in the management of spinal muscular atrophy

Fiona Moultrie [1,2,*], Laura Chiverton [1,2], Isabel Hatami [1,2], Charlotte Lilien [1,2], and Laurent Servais [1,2,3,*]

Spinal muscular atrophy (SMA) is a devastating, degenerative, paediatric neuromuscular disease which until recently was untreatable. Discovery of the responsible gene 30 years ago heralded a new age of pioneering therapeutic developments. Three disease-modifying therapies (DMTs) have received regulatory approval and have transformed the disease, reducing disability and prolonging patient survival. These therapies – with distinct mechanisms, routes of administration, dosing schedules, side effect profiles, and financial costs – have dramatically altered the clinical phenotypes of this condition and have presented fresh challenges for patient care. In this review article we discuss potential strategies to maximise clinical outcomes through early diagnosis and treatment, optimised dosing, use of therapeutic combinations and state-of-the-art physiotherapy techniques, and the development of innovative therapies targeting alternative mechanisms.

Highlights

Three disease-modifying therapies (DMTs) have revolutionised the care of patients with spinal muscular atrophy. However, outcomes are dependent upon treatment timing and disease severity.

Newborn screening programmes are essential to facilitate early diagnosis and treatment, improving patient outcomes.

Combinations of DMTs are used in practice and appear safe and tolerated, yet there is no evidence to date of benefit. Trials are ongoing.

Drugs targeting survival motor neuron-independent mechanisms show promise and potential synergistic benefits in preclinical studies and early trials. Clinical trials will determine their efficacy as add-on therapies.

Physiotherapy remains a cornerstone of management. Innovative techniques are being investigated which may optimise the functional gains of DMT-treated patients.

From gene to therapy

Thirty years ago the survival motor neuron (SMN) gene was identified as the gene responsible for SMA [1,2], a devastating, rare, progressive neuromuscular disease of childhood that affects approximately one in every 14 300 newborns [3]. At the time, there was no treatment, and SMA was the leading heritable cause of infant mortality. Homozygous mutations in the SMN1 gene on chromosome 5 (5q13) were found to prevent the expression of **SMN protein** (see Glossary), leading to degeneration of alpha motor neurons, progressive weakness, and ultimately death. The remarkably broad spectrum of clinical phenotypes – ranging from severe congenital to mild adult-onset forms – was categorised into five types, initially based upon a child's highest attainment of motor function and age at symptom onset [4] . Subsequently, the importance of the paralogue *SMN2* gene was discovered, and the inverse relationship between *SMN2* gene copy number and phenotypic severity [5]. Identification of the causative gene facilitated more accurate diagnosis and prognostication, and provided a promising target for therapeutic interventions.

In the past decade, three **DMTs** have been approved by the US FDA and the European Medicines Agency (EMA), which increase SMN protein expression through **gene therapy** (onasemnogene abeparvovec), **antisense oligonucleotides** (nusinersen), or modification of SMN2 splicing (small-molecule risdiplam). These ground-breaking therapies revolutionised the clinical landscape, improving survival, disability, and the quality of life of patients, and ultimately redefined SMA as a treatable condition. Children with SMA now have the potential to achieve normal or near-normal neurodevelopment if treated soon after birth. However, treatment outcomes are heterogeneous and greatly dependent upon a patient's *SMN2* copy number, clinical status, and surviving motor neurons at initiation of treatment [6]. Therefore, treated patients may continue to experience motor deficits and associated disease sequelae. Indeed, this complex evolving treatment landscape has resulted in novel clinical phenotypes and trajectories, presenting new challenges for patient care. Serious questions remain regarding optimisation and tailoring of

[1]MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, OX3 9DU, UK
[2]NIHR Oxford Biomedical Research Centre, Oxford, OX3 9DU, UK
[3]Neuromuscular Centre, Division of Paediatrics, University Hospital of Liège and University of Liège, 4000, Liège, Belgium

*Correspondence:
Fiona.moultrie@paediatrics.ox.ac.uk (F. Moultrie) and
Laurent.servais@paediatrics.ox.ac.uk (L. Servais).

treatments, and development of add-on therapies to further improve functional outcomes and quality of life for these children.

In this review we explore the promising future direction of SMA management, including the optimisation of the use of approved therapeutics and the integration of new treatment options. Firstly, we discuss the imperative of early diagnosis and treatment to maximise the therapeutic effects of both approved and future DMTs. This can be achieved only through the widespread adoption of efficient **newborn screening** programs. Secondly, we consider the potential benefits of combinations of DMTs to increase their efficacy, reviewing the latest evidence to date from trial and real-world data. Thirdly, we discuss the novel therapies on the horizon which could complement current therapies and address residual disease sequelae by exploiting novel targets such as myostatin, the neuromuscular junction, and epigenetic mechanisms. Lastly, we examine state-of-the-art advances in physiotherapy and non-pharmacological interventions, a perpetually enduring pillar of SMA management. In summary, the revolutionary impact of SMN-restoring therapies is undoubtable. However, further progress is necessary and achievable through pre-symptomatic diagnosis and treatment, combinations of SMN-restoring and emerging SMN-independent therapies, comprehensive investigation of novel phenotypes and non-responders, and the translation of promising preclinical therapies targeting novel mechanisms.

Timing is everything: newborn screening

The timing of treatment with DMTs affects the potential to optimise functional outcomes, particularly in patients with the most severe phenotypes. In mice, SMN-restoring therapies are relatively ineffective when administered beyond postnatal day 5. Meta-analysis of preclinical studies of SMA mouse models provides robust evidence that early treatment with DMTs has the greatest impact on survival [7]. Furthermore, antenatal administration may yield the greatest potential benefit [8]. Clinically, pre-symptomatic treatment can result in children who would never have walked acquiring near age-appropriate motor milestones [9–11]. Given that early treatment requires early diagnosis, newborn screening has the potential to further redefine SMA (Table 1). Recently, a non-randomised controlled trial demonstrated the effectiveness of SMA newborn screening in

Table 1. Evidence for SMA screening techniques

Intervention	Principle	Strengths	Weaknesses/limitations	Refs
PCR-based newborn screening	PCR-based testing for *SMN1* copy number in newborns	Potential for rapid turnaround Detection of 95% of SMA	Failure to detect point mutations and other rare pathogenic variants	[12]
Whole-gene sequencing newborn screening	Next-generation whole-gene-based sequencing in newborns	Detection of point mutations and other pathogenic variants undetected by PCR	Longer time to diagnosis	[19]
Prenatal diagnosis	Analysis of foetal DNA from chorionic villus sampling or amniocentesis. Or non-invasive prenatal testing using cell-free foetal DNA (cffDNA) in maternal plasma	Potential for earlier treatment at birth and consideration of premature delivery	Invasive testing associated with risk of miscarriage	[22]
Carrier screening	Pre-conception testing of prospective parents for SMN1 copies using quantitative PCR	Enables reproductive decision-making pre-conception	Cannot detect silent carriers (two SMN1 copies on same allele) or predict de novo mutations (2%) Can disregard for results Cultural, social and religious barriers	[24]

Glossary

Antisense oligonucleotides: short, synthetic, single-stranded oligodeoxynucleotides that bind to RNA in a target-specific manner to modify protein expression.
Body weight support harness: a harness suspended from the ceiling or external structure which supports a percentage of a user's body weight during standing, walking, or exercise. This system is commonly used in neuromotor rehabilitation.
Carrier screening: genetic testing offered to reproductive couples to determine whether they are carriers of an autosomal recessive or X-linked disease, which could affect their offspring.
Disease modifying therapy (DMT): a treatment that delays, slows, or reverses the progression of a disease by targeting the underlying pathophysiology.
Epigenetic regulation: biochemical mechanisms that turn gene expression on and off through alteration of the chemical structures of histones and DNA (e.g., histone acetylation, DNA methylation), without changing the underlying DNA sequence. It is a fundamental mechanism of environmental adaptation.
Gene editing: a form of gene therapy in which changes are made to the native genome of a living organism, such as by insertion, deletion, or replacement of a particular DNA sequence. This technique can treat single-gene disorders.
Gene therapy: a technique that alters an individual's genes (through replacement, inactivation, or introduction of a new gene) to treat or cure disease. In SMA, onasemnogene abeparvovec consists of an adeno-associated virus type 9 (AAV9) carrying complementary DNA encoding the SMN1 protein.
Hybrid assistive limb: a limb exoskeleton that uses skin sensors to detect bioelectrical signals generated by the wearer's muscle activity and amplifies intended movements. Trialled in neurorehabilitation of patients with stroke, spinal cord injury, cerebral palsy, and neuromuscular diseases.
Newborn screening: testing performed for the pre-symptomatic detection of infants with congenital disease. For SMA, DNA isolated from a dry blood drop is analysed most using qRT-PCR techniques for homozygous deletion of the SMN1 gene. A diagnostic

a real-world setting, importantly comparing clinical outcomes against those of unscreened patients [12]. Overall, 64% of children who were screened and received early treatment developed independent ambulation compared with 15% of children treated post-symptomatically, clearly demonstrating the power of early intervention.

SMA newborn screening programmes have been implemented across 72% of Europe and in at least six other countries worldwide [3,13–15]. However, many countries, including developed countries such as the UK, have not yet established a national programme [16]. This is despite overwhelming clinical benefit and cost-effectiveness. For the UK National Health Service (NHS), recent health economic analyses have determined that implementation could result in a projected £62million of yearly savings [17].

Nevertheless, there are challenges involved in screening that remain to be addressed. First, standard **PCR**-based testing detects *SMN1* gene deletions, accounting for ~95% of cases [18]. Detection of *SMN1* point mutations requires whole-gene sequencing, which has a longer turnaround time and therefore delays treatment. However, advances in next-generation sequencing (NGS) could make this approach feasible [19]. Second, there is significant variability, both between and within programs, in the turnaround time (from 2.7 days [13] to 2 weeks [14]), and mean age at treatment (21–45 days for two SMN2 copies; 24–133 for three SMN2 copies) [3]. Minimising the time to treatment is imperative to reduce death and disability. Rapid confirmation of results, excellent collaboration and communication between genetic and neuromuscular departments, and a clearly defined clinical pathway are imperative to maximise efficiency and efficacy of these programs [20].

Although early treatment undoubtedly increases functional gains, pathogenic changes can begin *in utero* [21]. Infants with the most severe phenotypes lose motor neurons from birth. In this case, newborn screening is insufficient, and the development of antenatal screening and *in vitro* treatments is necessary [22]. **Carrier screening** could also provide parents with the opportunity to make informed reproductive decisions [23]. However, a trial of carrier screening in Israel did not alter the rate of postnatal diagnoses [24]. This was attributed to social, cultural, and religious factors, which may limit the potential benefits of such programmes. Carrier screening is further limited by its bias due to greater engagement from higher socioeconomic classes [25] and its failure to identify patients with neo-mutations, such as in cases of false paternity or silent carriers with two copies of SMN1 on the same allele.

Overall, despite the challenges of newborn screening, the benefits are clear, and it is now imperative that all countries in which DMTs are available provide newborn screening programmes to facilitate pre-symptomatic diagnosis and treatment of patients within the optimal therapeutic window, maximising their clinical outcomes.

Shifting and adding DMTs

The DMTs approved for SMA include an antisense oligonucleotide (nusinersen), gene replacement therapy (onasemnogene abeparvovec, OA), and a small-molecule modifying SMN2 splicing (risdiplam). To date, clinical trials and observational studies have provided strong evidence of their efficacy (Box 1). These therapies differ in their mechanisms, routes of administration, dosing schedules, side effect profiles, and financial costs. Indeed, significant outstanding questions remain regarding the superiority of one drug over another and optimal dosing. There have been attempts to indirectly compare the outcomes of patients receiving nusinersen, risdiplam, and gene therapy [26–28]. However, conclusions are limited given the rarity and heterogeneity of this patient population. Without randomised superiority trials, it is impossible to definitively determine whether one DMT is more effective than another.

test is required for confirmation in positive cases.

Non-invasive spinal cord stimulation: a technique in which surface electrodes placed on the skin deliver pulses of electrical activity (5–10 Hz) to excite spinal cord afferents and stimulate motor neuron activity. In SMA, it has been trialled to support muscle activation during physical therapy.

PCR: a common laboratory technique used to amplify DNA sequences. Short synthetic DNA fragments (primers) are used to select a DNA segment, and multiple rounds of DNA synthesis are performed to produce millions of copies.

Standard of care: treatments and practices that are generally accepted and widely used by the medical community for the management of a disease.

Survival motor neuron (SMN) protein: a ubiquitous cellular protein involved in RNA metabolism, cytoskeletal maintenance, transcriptional regulation, cell signalling, and telomerase regeneration.

Box 1. Evidence for current disease modifying therapies

Nusinersen, an intrathecally administered synthetic antisense oligonucleotide, was the first DMT to receive regulatory approval. Through alternative splicing of the SMN2 gene, it increases the synthesis of transcripts containing exon 7, producing functional full-length SMN protein. Two Phase 3 clinical trials, ENDEAR (NCT02193074[xv]) and CHERISH (NCT02292537[xvi]), provided ground-breaking evidence that children with SMA types 1 and 2 could acquire clinically meaningful motor milestones never achieved by children receiving placebo [90,91]. Studies have continued to demonstrate sustained improvement in motor, respiratory, and survival outcomes, with the greatest effect when initiated pre-symptomatically [92].

The second approved DMT was an AAV9-based gene replacement therapy, OA, delivered by a single intravenous administration to children under 2 years of age. The START trial (NCT02122952[iv]) demonstrated that SMA type 1 patients receiving the highest dose had longer survival, greater achievement of motor milestones, and better motor function than historical controls [93]. Subsequent expedited Phase 3 trials in symptomatic SMA type 1 patients (STR1VE-US NCT03306277[xvii] and STR1VE-EU NCT03461289[xviii]) demonstrated sustained improvements in motor function, although hepatoxicity-related adverse events were common [94,95]. Furthermore, in the SPR1NT trial (NCT03505099[xix]), all pre-symptomatic infants developed the ability to sit independently by 18 months [9,10] (n = 14).

The third approved DMT was an orally administered small-molecule drug, risdiplam, which promotes inclusion of exon 7. The safety and efficacy of risdiplam was demonstrated in infants with type 1 SMA [96] (FIREFISH NCT02913482[xx]) and children, teenagers, and adults with types 2 and 3 SMA, with stabilisation of function in older patients (SUNFISH NCT02908685[xxi] [97]). The ongoing RAINBOWFISH trial (NCT03779334[xxii]) is investigating its efficacy in pre-symptomatic genetically diagnosed infants and has yielded promising results, with >80% of infants able to sit unsupported at 12 months [98].

Various DMT combinations have been given in trials and clinical practice (Table 2). Patients who respond incompletely to gene therapy could potentially benefit from add-on therapy with nusinersen or risdiplam. However, given that SMN protein expression decreases with age, there may be limited potential for a cumulative effect of sequential administration. The initial safety and tolerability of administering risdiplam to patients previously treated with other DMTs has been reported in a Phase 2, open-label clinical trial (JEWELFISH NCT03032172[i] [29,30]). Phase 4 open-label studies are under way to assess the effectiveness and safety of risdiplam (HINALEA 1 NCT05861986[ii]) and nusinersen (RESPOND NCT04488133[iii] [31]), when administered early after gene therapy.

Nusinersen and risdiplam are increasingly used as bridge therapies prior to gene therapy. Infants identified through newborn screening with elevated AAV9 antibody titres (>1:50) cannot be treated immediately with OA. However, they may benefit from loading doses of nusinersen or risdiplam prior to receiving gene therapy once antibody titres fall below threshold. This combination is used in clinical practice [32], and cases have been reported [33]. Although it is commonly accepted that DMTs should be administered as early as possible, there is no comparative study that formally demonstrates the benefits of this approach.

Longer courses of nusinersen or risdiplam prior to gene therapy, termed switch therapy, are also used in practice. Some patients in the Phase 1 trial of gene therapy (START NCT02122952[iv]) had received nusinersen prior to gene therapy (n = 7/13) although no comparative analysis of outcomes was performed. Improvements in motor function were reported, but interestingly the two patients who achieved standing had not received the combination [34]. Small retrospective studies have also reported outcomes following this combination, but none provided evidence of benefit [35–37].

In summary, despite the adoption of therapeutic combinations in clinical practice, only small, observational, single-arm, unblinded studies have been conducted. These provide limited evidence of safety and no evidence of superiority to monotherapy (for review see [38]). They do provide an important treatment option for patients awaiting gene therapy. Large-scale systematic

Table 2. Evidence for pharmacological therapies in the treatment of SMA

Intervention	Principle	Strengths	Weaknesses/limitations	Refs
DMT combinations				
Add-on therapy	Addition of second DMT after incomplete or suboptimal response to the first DMT	Phase 4 open-label studies in progress Risdiplam after DMT safe and tolerated (JEWELFISH: interim analysis) Nusinersen after gene therapy safe (RESPOND: initial result)	No available evidence of benefit SMN protein declines with age, limiting potential for cumulative effect	[29,31]
Bridge therapy	Nusinersen or risdiplam given whilst patient awaiting gene therapy	Used in clinical practice Newborns with raised AAV9 antibody titres could benefit	No randomised controlled trials	[32,33]
Switch therapy	Changing from one DMT to another in attempt to optimise outcomes	Used in clinical practice	No evidence of benefit in small studies to date	[34,37]
New pharmacological therapies				
Class 1 histone deacetylase (HDAC) inhibitors	Histone acetylation controls SMN expression	Repurposed drugs used in other diseases (e.g., valproic acid and sodium phenylbutyrate) Valproic acid: improvement in motor function on meta-analysis of ten studies	Valproic acid: no increase in survival on meta-analysis Sodium phenylbutyrate: several trials terminated (poor compliance or recruitment)	[39,40]
Neuroprotective agents	Mitochondrial membrane permeability to increase cell survival (Olesoxime) Reduction in excitotoxicity through glutamate receptor antagonism (Riluzole) or voltage-gated calcium channel inhibition (Gabapentin)	Olesoxime: safe and well tolerated in Phase 2/3 trials Riluzole: prolongs life expectancy in ALS Attenuates progression in mouse model Gabapentin: used in ALS	Olesoxime: no change in motor function over 24 months Riluzole: no results published from trial Gabapentin: improvement in limb strength reported in only one of two Phase 2/3 trials	[44,45] [41,42] [46,47]
Myostatin inhibitors	Inhibition of myostatin, a negative muscle bulk regulator	Three drugs in Phase 3 clinical trials Apitegromab (SAPPHIRE) Taldefgrobep alfa (RESILIENT) GYM329 (MANATEE)	Failure in other neuromuscular disorders May not benefit patients with advanced disease	[50–52]
Other muscle-targeted therapies	Fast skeletal muscle troponin activators increasing muscle contractility (Reldesemtiv) Synthetic growth factor increasing insulin growth factor-1 expression (somatotropin)	Increased peak expiratory pressure in Phase 2 trial	Reldesemtiv: no improvement in motor outcomes Somatotropin: no improvement in muscle function or strength	[56] [55]
Salbutamol	β2-adrenergic agonist increasing *SMN2* full-length transcript levels (promoting exon 7 inclusion)	Safe and well tolerated	Efficacy to be determined. Only 50% responded in trial of adults with SMA type 3	[59–61]
Pyridostigmine	Acetylcholinesterase inhibitor enhancing neuromuscular junction transmission	Safe and well tolerated. Enhanced low-threshold motor unit function in upper limb surface EMG Patient-reported reduction in fatigability	No effect on clinical assessment of fatigability and motor function (nine-hole peg test)	[62,63]
NMD670 - ClC-1 chloride channel inhibitor	Selective inhibition of the skeletal muscle chloride channel 1 (ClC-1)	Phase 2, randomised, double-blind, placebo-controlled, two-way crossover study ongoing to evaluate the efficacy, safety, and tolerability in adults with type 3 SMA	SYNAPSE-SMA^{X}; NCT05794139	
Small molecules targeting epigenetic regulatory proteins	Type I protein methyltransferases inhibitor (MS023) promoting exon 7 inclusion in *SMN2* pre-mRNA	Improves phenotype in SMA mouse model and acts synergistically to amplify effects of nusinersen	Only preclinical data. Human adverse effects unknown	[73]
CRISPR-Cas9 gene editing	Aims to restore endogenous gene expression and preserve native SMN regulation	Potential for future one-time curative treatment Preclinical studies show increased SMN protein levels, lifespan, and motor function	Only preclinical data Human adverse effects unknown	[74,75]

retrospective analysis of pooled patient data from international registries could provide evidence for the benefits and risks. A classification of disease-modifying treatment combinations has been proposed, which will be applied to explore safety and efficacy outcomes of patients in the RESTORE registry [32]. Ultimately, large multicentre randomised controlled trials with groups treated in parallel are necessary to determine superiority and, importantly, to identify patients likely to benefit from these approaches.

Targeting new mechanisms

Patients treated with DMTs continue to experience variable degrees of disease progression. Targeting alternative disease mechanisms beyond SMN depletion is likely necessary and complementary (Table 2). Potential targets include neuroprotective mechanisms, muscle growth factors, and neuromuscular junction function.

Histone acetylation controls SMN expression. Therefore, class 1 histone deacetylase (HDAC) inhibitors such as valproic acid and sodium phenylbutyrate used in cancer treatment have been repurposed and trialled in patients with SMA, with some improvement in motor function [39]. They may prove beneficial in combination with DMTs [40].

Neuroprotective agents promoting motor neuron survival have been investigated. Riluzole, a glutamate receptor antagonist that prolongs survival in amyotrophic lateral sclerosis (ALS) [41], proved effective in a preclinical model of SMA [42] and promising in a Phase 1 trial [43]. However, the results of a subsequent multicentric, randomised, double-blind trial in children with SMA types 2 and 3 have not been published (NCT00774423[v]). Similarly, olesoxime, a modulator of mitochondrial membrane permeability that promotes cell survival, showed early promise [44] that has not translated to success in later randomised controlled trials [45]. Gabapentin, a neuroprotective agent that reduces glutamate excitotoxicity, has also yielded little effect on motor function in clinical trials [46,47].

DMTs do not fully address the weakness and atrophy of muscles that have already become partially denervated prior to treatment. Given that myostatin negatively regulates skeletal muscle mass [48], anti-myostatin drugs have the potential to increase muscle bulk and strength to further improve function. Treatment with apitegromab (SRK-015), a human immunoglobulin G4 monoclonal antibody that inhibits myostatin activation, produced sustained improvement in motor function at 36 months in patients with types 2 and 3 SMA in a Phase 2 randomised open-label trial (TOPAZ NCT03921528[vi] [49,50]). The non-peer-reviewed topline results of the Phase 3 double-blind placebo-controlled trial (Sapphire NCT05156320[vii]) have now been released, indicating a 1.8-point ($P = 0.0192$) difference in the Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) between treated (with either 10 or 20 mg/kg) and placebo patients aged 2–12 years[viii]. Similarly, a multicentre, Phase 3, double-blind, placebo-controlled trial (RESILIENT NCT05337553[ix]) is investigating the safety and efficacy of taldefgrobep alfa, a novel, fully human anti-myostatin adnectin recombinant protein that competitively inhibits myostatin and activin A [51]. This mechanistically distinct approach could minimise off-target effects resulting from activin type II receptor blockage in non-muscle tissue. The non-peer-reviewed topline results of the trial have now been released, indicating clinically meaningful improvements in motor function – measured using the Motor Function Measurement-32 scale (MFM-32) at all timepoints – and excellent target engagement. However, the primary outcome, a difference between untreated and treated patients at week 48, was only statistically significant in patients with detectable myostatin at baseline[x]. Lastly, the combination of risdiplam with an anti-latent myostatin sweeping antibody, which eliminates latent myostatin from plasma and tissue, is currently being investigated in a Phase 3 multicentre, two-part, randomised, placebo-controlled, double-blind study

in treatment-naïve and non-treatment-naïve patients [52] (MANATEE NCT05115110[xi]). Unfortunately, the potential benefits of anti-myostatins may be limited. Despite their promise in preclinical models [53], this therapy has been unsuccessfully trialled in other neuromuscular conditions, including Duchenne, inclusion body myositis, and facioscapulohumeral muscular dystrophy. In SMA, myostatin is naturally downregulated, and circulating levels decrease significantly with age and baseline function [54]. Furthermore, it seems that 1 year of treatment with nusinersen does not increase myostatin levels in SMA patients [54]. Therefore, it is unclear whether patients with advanced disease would benefit. Other muscle targets have been identified, but clinical trials of synthetic somatotropin [55] and a fast skeletal-muscle troponin activator (reldesemtiv) did not report positive effects on motor outcomes [56].

Growing evidence indicates that structural and functional abnormalities of the neuromuscular junction contribute significantly to the disease [57] and may underlie the fatiguability reported by patients [58]. Therapies targeting neuromuscular transmission may further optimise patient outcomes. Salbutamol, a short-acting β_2 adrenergic receptor agonist classically used to treat asthma, increases full-length SMN2 transcripts both *in vitro* and *in vivo*. It is given off-label in many centres based on evidence from open-label pilot studies and a double-blind randomised trial in adults with SMA type 3 [59–61]. Despite reports of improved functional scores, placebo-controlled trials are needed to fully determine the efficacy of this treatment. Similarly, pyridostigmine, an acetylcholinesterase inhibitor used to treat myasthenia gravis, is being investigated. Patients with SMA receiving pyridostigmine have enhanced low-threshold motor unit function in upper limb muscles on surface electromyography (EMG) [62]. In a Phase 2 monocentric, placebo-controlled, double-blind, crossover trial in treatment-naïve patients, although there were no significant differences in primary outcomes, self-reported reductions in fatigability may indicate potential benefit (SPACE NCT02941328[xii] [63]). Following favourable safety outcomes in Phase 1 testing [64], a muscle-specific chloride channel inhibitor, NMD670, is also being investigated in a Phase 2 randomised double-blind placebo-controlled crossover study in adults with type 3 SMA (SYNAPSE-SMA NCT05794139[xiii]).

Other disease mechanisms have been identified in preclinical models of SMA, providing novel targets for future therapeutic clinical trials. These include preventing the degradation of SMN protein [65], targeting SMN's pivotal role in translation and protein homeostasis [66], cytoskeletal dysregulation and the RhoA-ROCK signalling pathway [67], endocytosis [68], autophagy [69], and ubiquitin homeostasis [70] (for review see [71]). **Epigenetic regulation** of gene expression is emerging as a novel therapeutic target [72]. Small-molecule inhibitors of proteins mediating epigenetic signalling – such as protein methyltransferases (PRMTs) – are showing positive results in preclinical models, promoting SMN2 exon 7 inclusion and acting synergistically with nusinersen [73]. Lastly, state-of-the-art **gene editing** techniques, such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9), offer the tantalising potential for curative treatment. These technologies are in the early stages of development and are yielding promising preclinical results [74,75].

In summary, SMN-independent therapies have the potential to provide additive or synergistic benefits for patients and may prove particularly important in maintaining motor function in patients as they get older.

The promise of non-pharmacological interventions

Alongside the introduction of DMTs, **standard of care** provided by a multidisciplinary care team is essential. Physiotherapy is a fundamental component which can improve patient quality of life and treat clinical sequelae that are not reversed by DMTs, such as scoliosis [76], contractures,

and respiratory impairment [77]. The current era of evolving phenotypes creates challenges for patient care, especially for patients treated after a clinically silent phase [78–80]. Therefore, management strategies, access, and set-up must evolve and diversify to address patient needs, regardless of initial treatment response. Respiratory muscle weakness can lead to repeated and life-threatening infections [77]. Recently, non-peer-reviewed results of the RESISTANT study (NCT05632666[xiv]) have been presented which suggest the feasibility and potential benefits of decentralised respiratory muscle strength rehabilitation [81]. Home-based rehabilitation reduces the logistical burden for patients and demand on the physiotherapy service.

Given that regular hands-on physiotherapy supports motor function [82], various innovative physiotherapy rehabilitation technologies using electrical stimulation, harnessing, and exoskeletons have been investigated in small case or cohort studies (Table 3). **Non-invasive spinal cord stimulation**, which is used in the rehabilitation of children with spinal cord injury and cerebral palsy, may benefit children with SMA. External electrical stimulation of motor neurons restored by DMT could theoretically facilitate the development of motor skills. Improvements in contractures, muscle strength, and forced lung capacity have been reported in a small case study over a 2-week period combined with physical therapy (n = 5) [83]. Combining electrotherapy with

Table 3. Evidence for non-pharmacological therapies in SMA management

Intervention	Principle	Strengths	Weaknesses/limitations	Refs
Hands-on physiotherapy	Increased frequency of hands-on physiotherapy	Closer patient follow-up Regular, targeted exercises Adaptation of rehabilitation goals	Staffing requirement Resources of state or family (for private) Geographical localisation Family commitment.	[82]
Respiratory rehabilitation	Respiratory muscle training	Individualised home-based program to ease access for patients and reduce staff limitation	Results to be published in a peer-reviewed journal	[81]
Non-invasive spinal cord stimulation and physical therapy	Non-invasive electrical stimulation of the spinal cord with bipolar or monopolar pulses (5–10 kHz)	New contractures may be targeted and increase/maintain ROM Needs further research	SMA type dependent Likely less tolerated by very young children	[83]
Electrotherapy and exercise	Multimodal approach based on electrotherapy and cycling exercise using the FES cycle-ergometer (Pegaso, Biotech, Italy)	Well tolerated. May improve motor performance Home-based program Reduces staff limitation Individualised settings	Supervision of settings. Space and access requirements. Further research needed	[84]
Body weight support harness	Body weight support harness system (BWSS) used at home	Home-based program Reduces staff limitation Safe, feasible Tolerated by families Potential to optimise gross motor abilities Suitable for very young children	Requires degree of head control Space and access requirements	[85]
Cyborg	Treatment provided with the cyborg hybrid assistive limb (HAL) gait training	Encouraging results in gait function Weight-bearing rehabilitation for adults is usually challenging Needs further research	Patient/family commitment Need other therapies Probably more suitable for SMA types with enough trunk control Developed for adults Expensive	[87]
Robot-assisted gait training	ATLAS 2030 exoskeleton for gait training	Suitable for children with at least head and trunk support (with or without brace) while standing and walking Contractures not contraindicated	Anthropometric and weight requirements (<35kg) Needs further research Expensive	[86]

exercise may confer additional benefits. A further case study reports enhanced motor function and range of motion in an adolescent patient with SMA type III [84].

Body weight support devices are also used in paediatric neurorehabilitation. These devices could accelerate motor skill acquisition by providing a partial weight-bearing environment. A novel multiplanar in-home **body weight support harness** system was trialled in a 6-month prospective cohort study of young children with types 1 and 2 SMA treated with DMTs. The technique appears safe, feasible, well tolerated, and may help to optimise function after pharmacological treatment [85].

Motor learning could further be supported by exoskeletons and robot-assisted gait training, which benefit children with cerebral palsy and spinal cord injuries. A small case study using the ATLAS 2030 described improvements in lower limb strength and range of motion in young children with SMA ($n = 3$) [86]. Similarly, the **hybrid assistive limb** for gait training was investigated in a multicentre, randomised, controlled, crossover trial [87]. Reported improvements in motor function are encouraging, although very few participants had SMA ($n = 5$).

Overall, these approaches offer the potential to optimise the functional gains of DMT-treated patients. The challenges faced in conducting large-scale efficacy studies in rehabilitation could be addressed by collecting real-world data from standardised and harmonised practices across countries. In addition, it will be essential to define which patient populations will benefit most from their implementation as baseline functional requirements will differ dramatically between techniques.

Concluding remarks

Over the past 30 years, SMA has become not only a treatable condition but an archetypal model of successful translation of genetic understanding to targeted and effective therapies. Regulatory approval of three mechanistically distinct disease-modifying drugs has transformed the treatment landscape (see Clinician's corner) and created novel and evolving clinical phenotypes. Earlier treatment is undoubtedly the most fundamental next step towards improving the prognosis for patients. As such, newborn screening programmes are of fundamental importance. Progress is being made, but programmes still require further optimisation, particularly in the determination of *SMN2* copy number. Nevertheless, given the evidence to date, adoption of screening programmes should occur as soon as possible in all countries that provide access to treatments. A step further would be to electively deliver infants prematurely for treatment at an earlier stage of motor neuron development. Prematurely born infants with SMA have now been safely and successfully treated with OA at 33 weeks' gestation [88]. However, elective late-preterm delivery for this purpose would require judicious assessment of the balance of the benefits of treatment versus the considerable risks of prematurity, which can vary greatly depending on gestational age. Additionally, there is the risk of treatment-related adverse effects such as immune-mediated effects requiring management with prednisolone, which is also associated with neurodevelopmental disorders. Critical questions remain unanswered regarding the superiority of individual DMTs and added benefits of combination and switch therapies (see Outstanding questions), which can only ultimately be addressed by further investment and significant patient engagement in high-quality prospective clinical trials. SMN-independent therapies that target other pathogenic processes will likely become a key component of standards of care, improving outcomes that cannot be addressed by current therapies. Despite the tremendous advances in pharmacological therapies and multidisciplinary care, physiotherapy remains a cornerstone of management for patients with SMA, and state-of the art innovations in physical rehabilitation will play an important role in addressing the evolving needs of this heterogeneous patient population.

Outstanding questions

Of the current approved DMTs (nusinersen, OA, and risdiplam), is one therapy superior in terms of functional and survival outcomes?

Should a foetus with two copies of *SMN2* be delivered prematurely to be treated as early as possible?

Are combinations of DMTs – such as switch, add-on, and bridge therapy – justified? Do they significantly improve patient outcomes compared with monotherapy?

Do anti-myostatin drugs significantly improve the outcomes of patients treated with DMTs?

How can we optimise current physiotherapy practices for patients treated with DMTs to maximise functional and respiratory outcomes? How can innovative rehabilitation devices support delivery of, access to, and efficacy of physiotherapy?

The future management of SMA will likely rely on a combination of prevention through carrier screening and/or newborn screening facilitating early treatment. Add-on therapies and assistive technologies will likely be used to complement initial SMN-restoring therapies. Whether cell therapies could eventually provide the opportunity for clinical improvement in patients who remain symptomatic despite SMN-restoring treatments (patients born prior to a newborn screening era or who are born with symptomatic disease) remains unknown. Regardless, given the heterogeneity of the patient population in terms of clinical condition and treatment history, clinical trials will become increasingly difficult to define and will necessitate innovative designs and outcomes such as continuous objective measures of movement [89] unless a very large therapeutic effect is anticipated.

Declaration of interests

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Resources

[i]https://clinicaltrials.gov/study/NCT03032172

[ii]https://clinicaltrials.gov/study/NCT05861986

[iii]https://clinicaltrials.gov/study/NCT04488133

[iv]https://clinicaltrials.gov/study/NCT02122952

[v]https://clinicaltrials.gov/study/NCT00774423

[vi]https://clinicaltrials.gov/study/NCT03921528

[vii]https://clinicaltrials.gov/study/NCT05156320

[viii]https://investors.scholarrock.com/news-releases/news-release-details/scholar-rock-reports-apitegromab-meets-primary-endpoint-phase-3

[ix]https://clinicaltrials.gov/study/NCT05337553

[x]www.prnewswire.com/news-releases/biohaven-provides-update-on-taldefgrobep-alfa-development-program-for-spinal-muscular-atrophy-and-obesity-302314979.html

[xi]https://clinicaltrials.gov/study/NCT05115110

[xii]https://clinicaltrials.gov/study/NCT02941328

[xiii]https://clinicaltrials.gov/study/NCT05794139

[xiv]https://clinicaltrials.gov/study/NCT05632666

[xv]https://clinicaltrials.gov/study/NCT02193074

[xvi]https://clinicaltrials.gov/study/NCT02292537

[xvii]https://clinicaltrials.gov/study/NCT03306277

[xviii]https://clinicaltrials.gov/study/NCT03461289

[xix]https://clinicaltrials.gov/study/NCT03505099

[xx]https://clinicaltrials.gov/study/NCT02913482

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[xxii]https://clinicaltrials.gov/study/NCT03779334

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