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Drug treatment for spinal muscular atrophy types II and III (Review)

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[Intervention Review]

Drug treatment for spinal muscular atrophy types II and III

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ABSTRACT

Background

Spinal muscular atrophy (SMA) is caused by a homozygous deletion of the *survival motor neuron 1* (*SMN1*) gene on chromosome 5, or a heterozygous deletion in combination with a (point) mutation in the second *SMN1* allele. This results in degeneration of anterior horn cells, which leads to progressive muscle weakness. Children with SMA type II do not develop the ability to walk without support and have a shortened life expectancy, whereas children with SMA type III develop the ability to walk and have a normal life expectancy. This is an update of a review first published in 2009 and previously updated in 2011.

Objectives

To evaluate if drug treatment is able to slow or arrest the disease progression of SMA types II and III, and to assess if such therapy can be given safely.

Search methods

We searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and ISI Web of Science conference proceedings in October 2018. In October 2018, we also searched two trials registries to identify unpublished trials.

Selection criteria

We sought all randomised or quasi-randomised trials that examined the efficacy of drug treatment for SMA types II and III. Participants had to fulfil the clinical criteria and have a homozygous deletion or hemizygous deletion in combination with a point mutation in the second allele of the *SMN1* gene (5q11.2-13.2) confirmed by genetic analysis.

The primary outcome measure was change in disability score within one year after the onset of treatment. Secondary outcome measures within one year after the onset of treatment were change in muscle strength, ability to stand or walk, change in quality of life, time from the start of treatment until death or full-time ventilation and adverse events attributable to treatment during the trial period.

Treatment strategies involving *SMN1*-replacement with viral vectors are out of the scope of this review, but a summary is given in Appendix 1. Drug treatment for SMA type I is the topic of a separate Cochrane Review.

Data collection and analysis

We followed standard Cochrane methodology.

Main results

The review authors found 10 randomised, placebo-controlled trials of treatments for SMA types II and III for inclusion in this review, with 717 participants. We added four of the trials at this update. The trials investigated creatine (55 participants), gabapentin (84 participants), hydroxyurea (57 participants), nusinersen (126 participants), olesoxime (165 participants), phenylbutyrate (107 participants), somatotropin (20 participants), thyrotropin-releasing hormone (TRH) (nine participants), valproic acid (33 participants), and combination therapy with valproic acid and acetyl-L-carnitine (ALC) (61 participants). Treatment duration was from three to 24 months. None of the studies investigated the same treatment and none was completely free of bias. All studies had adequate blinding, sequence generation and reporting of primary outcomes.

Based on moderate-certainty evidence, intrathecal nusinersen improved motor function (disability) in children with SMA type II, with a 3.7-point improvement in the nusinersen group on the Hammersmith Functional Motor Scale Expanded (HFMSE; range of possible scores 0 to 66), compared to a 1.9-point decline on the HFMSE in the sham procedure group ($P < 0.01$; n = 126). On all motor function scales used, higher scores indicate better function.

Based on moderate-certainty evidence from two studies, the following interventions had no clinically important effect on motor function scores in SMA types II or III (or both) in comparison to placebo: creatine (median change 1 higher, 95% confidence interval (CI) –1 to 2; on the Gross Motor Function Measure (GMFM), scale 0 to 264; n = 40); and combination therapy with valproic acid and carnitine (mean difference (MD) 0.64, 95% CI –1.1 to 2.38; on the Modified Hammersmith Functional Motor Scale (MHFMS), scale 0 to 40; n = 61).

Based on low-certainty evidence from other single studies, the following interventions had no clinically important effect on motor function scores in SMA types II or III (or both) in comparison to placebo: gabapentin (median change 0 in the gabapentin group and –2 in the placebo group on the SMA Functional Rating Scale (SMAFRS), scale 0 to 50; n = 66); hydroxyurea (MD –1.88, 95% CI –3.89 to 0.13 on the GMFM, scale 0 to 264; n = 57), phenylbutyrate (MD –0.13, 95% CI –0.84 to 0.58 on the Hammersmith Functional Motor Scale (HFMS) scale 0 to 40; n = 90) and monotherapy of valproic acid (MD 0.06, 95% CI –1.32 to 1.44 on SMAFRS, scale 0 to 50; n = 31).

Very low-certainty evidence suggested that the following interventions had little or no effect on motor function: olesoxime (MD 2, 95% –0.25 to 4.25 on the Motor Function Measure (MFM) D1 + D2, scale 0 to 75; n = 160) and somatotropin (median change at 3 months 0.25 higher, 95% CI –1 to 2.5 on the HFMSE, scale 0 to 66; n = 19). One small TRH trial did not report effects on motor function and the certainty of evidence for other outcomes from this trial were low or very low.

Results of nine completed trials investigating 4-aminopyridine, acetyl-L-carnitine, CK-2127107, hydroxyurea, pyridostigmine, riluzole, RO6885247/RG7800, salbutamol and valproic acid were awaited and not available for analysis at the time of writing.

Various trials and studies investigating treatment strategies other than nusinersen (e.g. SMN2-augmentation by small molecules), are currently ongoing.

Authors' conclusions

Nusinersen improves motor function in SMA type II, based on moderate-certainty evidence.

Creatine, gabapentin, hydroxyurea, phenylbutyrate, valproic acid and the combination of valproic acid and ALC probably have no clinically important effect on motor function in SMA types II or III (or both) based on low-certainty evidence, and olesoxime and somatropin may also have little to no clinically important effect but evidence was of very low-certainty. One trial of TRH did not measure motor function.

PLAIN LANGUAGE SUMMARY

Medicines for spinal muscular atrophy types II and III

What was the aim of this review?

This Cochrane Review aimed to look at the effects of medicines on spinal muscular atrophy (SMA) types II and III in terms of disability, muscle strength, ability to stand or walk, quality of life, and time to death or full-time ventilation, within one year of beginning treatment. We also wanted to identify any harmful effects of the treatments during the trial period. Cochrane review authors collected relevant studies to answer this question and found 10 studies.

Key messages

Nusinersen given by intrathecal (into the spine) injection probably improves disability in SMA.

Creatine, phenylbutyrate, gabapentin, hydroxyurea, valproic acid and combination therapy with valproic acid and acetyl-L-carnitine probably have no clinically important effect on motor function (movements and actions of the muscles) in SMA types II and III, based on evidence from single completed, published trials.

Olesoxime and subcutaneous somatotropin may have little or no effect on motor function in SMA, but the reliability of the evidence was very low. One trial of intravenous (into a vein) thyrotropin-releasing hormone (TRH) did not measure motor function and the reliability of the evidence was very low. All the studies had limitations in design or performance that could have affected the results.

What was studied in the review?

This review is of medicines for SMA types II and III. Symptoms of SMA first appear in childhood and adolescence. The main feature is increasing muscle weakness. Children with SMA type II will never be able to walk without support; they usually live into adolescence or longer, but with a shortened life expectancy. The age of onset of SMA type II is between six and 18 months. Children with SMA type III will walk independently but may lose the ability to walk at some time and they have a normal life expectancy. The age of onset of SMA type III is after 18 months.

What were the main results of the review?

We identified 10 trials, which included 717 participants. All trials compared a medicine with an inactive substance (placebo) or sham (pretend) procedure. The trials studied oral (by mouth) creatine (55 participants), oral gabapentin (84 participants), oral phenylbutyrate (107 participants), oral hydroxyurea (57 participants), intrathecal nusinersen (126 participants), oral olesoxime (165 participants), subcutaneous (under the skin) somatotropin (20 participants), intravenous TRH (nine participants), oral valproic acid (33 participants) or combination therapy with oral valproic acid and acetyl-L-carnitine (ALC) (61 participants). Treatment duration was from three to 24 months.

Nusinersen had a beneficial effect on motor function in people with SMA type II, when compared to a sham procedure. There were probably no beneficial effects on motor function in SMA types II/III for creatine, gabapentin, hydroxyurea, phenylbutyrate, valproic acid or combination therapy with valproic acid and ALC. Olesoxime and somatotropin may have no effect on motor function. The small TRH trial did not assess motor function and did not provide evidence of any reliability on other outcomes. We found all the studies to have limitations in design or performance that could have affected the results. Eight studies were (partially) funded by pharmaceutical companies, either by supplying the study drug or by giving financial support otherwise. In two studies investigating nusinersen and olesoxime, the pharmaceutical companies were involved in data analysis and reporting.

We are awaiting the results of nine completed trials investigating 4-aminopyridine, ALC, CK-2121707 hydroxyurea, pyridostigmine, riluzole, RO6885247/RG7800, salbutamol and valproic acid which were not available at the time of writing.

How up to date is this review?

The evidence is up to date to October 2018.

Summary of findings for the main comparison. Oral creatine compared to placebo for children with SMA types II and III

Oral creatine compared to placebo for children with SMA types II and III

Patient or population: children with SMA types II and III
Setting: outpatient clinic
Intervention: oral creatine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral creatine				
Change in disability score assessed with: GMFM Scale: 0–264 Follow-up: 9 months	The median change in disability score was –1	**Median change 1 higher** (1 lower to 2 higher)	—	40 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
Change in total muscle strength (total muscle strength) assessed with: quantitative muscle testing (in pounds) Follow-up: 9 months	The mean change in total muscle strength was 2.42 pounds	**MD 1.25 pounds lower** (10.1 lower to 7.6 higher)	—	22 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	Only participants aged ≥ 5 years.
Acquiring the ability to stand or walk	Not measured					
Change in quality of life assessed with: Parent Questionnaire for the PedsQL Neuromuscular Module Scale: 0–100 Follow-up: 9 months	The median change in quality of life was 2	**Median change 7 lower** (11 lower to 3 higher)	—	38 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the PedsQL indicate better quality of life.
Change in pulmonary function	The mean change in pulmonary function was –0.83 % predicted	**MD 0.56 % predicted higher** (10.8 lower to 11.9 higher)	—	23 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	Only participants aged ≥ 5 years.

assessed with: FVC (in % predicted) Follow-up: 9 months						
Time from beginning of treatment until death or full-time ventilation	1 death occurred in the placebo group in 28 participants (36 per 1000)	0 deaths occurred in the treatment group among 27 participants (0 per 1000)	—	40 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
Adverse events related to treatment	571 per 1000	480 per 1000 (291 to 800)	**0.84** (0.51 to 1.4)	40 (1 RCT)	⊕⊕⊖⊖ **Low**[d,e]	There were 43 events in 16/28 participants in placebo group and 55 events in 13/27 participants treated with creatine. Adverse events were systematically, prospectively collected at every study visit. Adverse events included mainly respiratory infections.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FVC:** forced vital capacity; **GMFM:** Gross Motor Function Measure; **MD:** mean difference; **MHFMS:** Modified Hammersmith Functional Motor Scale; **MMT:** Manual Muscle Testing; **PedsQL:** Pediatric Quality of Life Inventory; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision because of the small sample size.
[b] Downgraded one level due to inconsistency. Unknown cohort representation (outcome reported for 22 of the randomised participants).
[c] Downgraded one level because of imprecision. Small sample size, inadequately for optimal information size (OIS). Cut off for OIS was the calculated sample size of the trial.
[d] Downgraded one level for risk of bias. No information on type of adverse events included.
[e] Downgraded one level for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 2. Oral gabapentin compared to placebo for adults with SMA types II and III

Oral gabapentin compared to placebo for adults with SMA types II and III

Patient or population: adults with SMA types II and III
Setting: outpatient clinic
Intervention: oral gabapentin

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral gabapentin				
Change in disability score assessed with: SMAFRS Scale: 0–50 Follow-up: 12 months	The median change in the SMAFRS score was 0 in the gabapentin group (37 participants) and –2 in the placebo group (34 participants)		—	66 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the SMAFRS indicate better function.
Change in muscle strength assessed as: % change in total muscle strength from baseline Follow-up: 12 months	The mean change in muscle strength was –2.2%	**MD 3.3% higher** (6.9 lower to 14 higher)	—	50 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Acquiring ability to walk Follow-up: 12 months	0/35 participants in the placebo group developed the ability to walk at 9 or 12 months' follow-up	0/38 participants treated with oral gabapentin developed the ability to walk at 9 or 12 months' follow-up	—	73 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Change in quality of life assessed with: change (%) from baseline in mini-SIP Scale: 0–19 Follow-up: 12 months	The mean change in quality of life was –0.26%	**MD 0.36% higher** (0.29 lower to 1 higher)	—	67 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the mini-SIP indicate poorer health status.
Change in pulmonary function assessed with: FVC (in % predicted) Follow-up: 12 months	The mean change in pulmonary function was –2.9 % predicted	**MD 1.1 % predicted lower** (4.1 lower to 1.9 higher)	—	65 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	Data from analysis of participants who completed ≥ 2 visits.

Time from beginning of treatment to death or full-time ventilation Follow-up: 12 months	0 reported deaths and 0 participants required full-time ventilation	—	84 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
Adverse events related to treatment Follow-up: median 12 months	Adverse events were reported to be infrequent and not statistically different between treatment groups. Numerical data on adverse events were not available.	—	65 (1 RCT)	⊕⊕⊖⊖ **Low**[d,e]	Adverse events were systematically, prospectively collected at every study visit.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FVC:** forced vital capacity; **MD:** mean difference; **mini-SIP:** mini-Sickness Impact Profile; **PedsQL:** Pediatric Quality of Life Inventory; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy; **SMAFRS:** Spinal Muscular Atrophy Functional Rating Scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision because the small sample size.
[b] Downgraded one level for risk of bias. Incomplete data at 12-month follow-up and it was unclear why cases dropped out. Three cases (two treated, one placebo) were excluded from analysis because of extreme outcomes (greater than three standard deviations).
[c] Downgraded one level because of imprecision; small sample size, inadequate for optimal information size (OIS).
[d] Downgraded one level because no data on adverse events were available.
[e] Downgraded one level for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 3. Oral hydroxyurea compared to placebo for children and adults with SMA types II and III

Oral hydroxyurea compared to placebo for children and adults with SMA types II and III

Patient or population: children and adults with SMA types II and III
Setting: outpatient clinic
Intervention: oral hydroxyurea
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral hydroxyurea				
Change in disability score assessed with: GMFM Scale: 0–264 Follow-up: 18 months	The mean change in disability score was 2.02	**MD 1.88 lower** (3.89 lower to 0.13 higher)	—	57 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the GMFM indicate better function.
Change in disability score assessed with: MHFMS Scale: 0–40 Follow-up: 18 months	The mean change in disability score was 0.04	**MD 0.02 lower** (0.12 lower to 0.07 higher)	—	38 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	Only performed in non-ambulatory participants.
Change in muscle strength assessed with: MMT Scale: 16–80 Follow-up: 18 months	The mean change in muscle strength was –0.03	**MD 0.55 lower** (2.65 lower to 1.55 higher)	—	57 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	—
Acquiring the ability to stand or walk	Not measured					
Change in quality of life	Not measured					
Change in pulmonary function assessed with: FVC (in litres) Follow-up: 18 months	The mean change in pulmonary function was –0.22 L	**MD 0.01 L higher** (0.25 lower to 0.26 higher)	—	57 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Time from beginning of treatment until death or full-time ventilation	1 participant died in the treatment group after 5 visits (after 8 months of treatment), due to respiratory complications.		—	57 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	Also reported as the 1 serious adverse event.
Adverse events related to treatment Follow-up: 18 months	All participants experienced adverse events. 129 events occurred in the 20 participants in the placebo group. 224 events occurred in the 37 participants in the hydroxyurea group.		—	57 (1 RCT)	⊕⊕⊕⊖ **Moderate**[d]	Adverse events were systematically, prospectively collected using a questionnaire at every study visit. Adverse events: laboratory disturbances (e.g. neutropenia, thrombocy-

						topenia, high transaminases), respiratory complaint, gastrointestinal complaints, rash, neurological symptoms, unspecified. 1 participant died in the treatment group due to respiratory complications.[d]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **FVC:** forced vital capacity; **GMFM:** Gross Motor Function Measure; **MD:** mean difference; **RCT:** randomised controlled trial; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision. CIs were very wide.
[b] Downgraded one level for imprecision because of small sample size (inadequate for optimal information size (OIS)). Cut-off for OIS was the calculated sample size of the trial.
[c] Downgraded one level for indirectness, because of discrepancy in results of respiratory failure (results in text and figures appeared different).
[d] Downgraded one level for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 4. Intrathecal injected nusinersen compared to sham procedure for children with SMA type II

Intrathecal injected nusinersen compared to sham procedure for children with SMA type II

Patient or population: children with SMA type II
Setting: hospital visits (24 hours' observation at trial site after first procedure, 6 hours' observation after subsequent injections)
Intervention: intrathecal injected nusinersen
Comparison: sham procedure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham procedure	Risk with intrathecal injected nusinersen				
Change in disability score assessed with: HFMSE Score: 0–66 Follow-up: mean 15 months	The mean change in HFMSE in the con-	The mean change in HFMSE in the nusinersen-treated group was 5.9 points high-	**MD 5.9** (3.7 to 8.1)	126 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	

		trol group was –1.9 points	er than in the sham procedure group (3.7 higher to 8.1 higher)				
Change in disability score (3 point-change) assessed with: HFMSE Follow-up: mean 15 months		262 per 1000	471 per 1000 (259 to 812)	**RR 1.8** (0.99 to 3.1)	126 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	11/42 participants in the sham-controlled group showed a 3-point change on the HFMSE. 48/84 participants in the nusinersen group showed a 3-point change on the HFMSE.
Change in muscle strength		Not measured					
Acquiring the ability to stand or walk assessed with: WHO Motor Milestone criteria Follow-up: 15 months	**Acquiring the ability to stand**	1/42 children in the sham-controlled group acquired the ability to stand alone.	1/84 children treated with nusinersen acquired the ability to stand alone.	**RR 0.5** (0.03 to 7.80)	126 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	
	Acquiring the ability to walk	0/42 children in the sham-controlled group acquired the ability to walk with assistance.	1/84 children treated with nusinersen acquired the ability to walk with assistance.	**RR 1.5** (0.06 to 36.1)	126 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	
Change in quality of life		Not measured					
Change in pulmonary function		Not measured					
Time from beginning of treatment until death or full-time ventilation		Not measured					
Adverse events related to treatment Follow-up: mean 15 months		1000 per 1000	900 per 1000	**RR 0.9** (0.9 to 1.0)	126 (1 RCT)	⊕⊕⊕⊖ **Moderate**[c]	78/84 (93%) participants treated with nusinersen experienced an adverse event, while 42/42 (100%) participants treated in the sham-controlled group had any adverse event.

						Adverse events were systematically, prospectively collected at every study visit. Adverse events included proteinuria, hyponatraemia, transient low platelet counts, vasculitis, pyrexia, headache, vomiting, back pain and epistaxis.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HFMSE:** Hammersmith Functional Motor Measure Expanded; **MD:** mean difference; **MHFMS:** Modified Hammersmith Functional Motor Scale; **MMT:** manual muscle testing; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy; **WHO:** World Health Organization.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for imprecision because of the small sample size.
[b] Downgraded two levels for imprecision because of small sample size, low event rate and wide CI.
[c] Downgraded one level for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 5. Oral olesoxime compared to placebo for non-ambulatory children and adolescents with SMA types II and III

Oral olesoxime compared to placebo for non-ambulatory children and adolescents with SMA types II and III

Patient or population: non-ambulatory children and adolescents with SMA types II and III
Setting: outpatient clinic
Intervention: oral olesoxime
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral olesoxime				

Change in disability score assessed with: MFM (D1+D2) Scale: 0–75 Follow-up: 24 months	The mean change in disability score was –1.82	**MD 2 higher** (0.25 lower to 4.25 higher)	—	160 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	Higher scores on the MFM indicate better function. Combined analysis of participants assessed with MFM-32 or MFM-20.
Change in disability score assessed with: MFM total score Scale: 0–96 Follow-up: 24 months	The mean change in disability score was –1.45	**MD 2.04 higher** (0.21 lower to 4.28 higher)	—	160 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	Higher scores on the MFM indicate better function. Combined analysis of participants assessed with MFM-32 or MFM-20.
Change in disability score assessed with: MFM responder analysis Follow-up: 24 months	**Study population** 39 per 100	55 per 100 (–38 to 80)	**RR 1.43** (–0.98 to 2.08)	160 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	Higher scores on the MFM indicate better function. Participants were classified as 'responders' in case MFM-32 or MFM-20 showed no change or better scores compared to baseline, and 'non-responders'.
Change in disability score assessed with: HFMS Scale: 0–40 Follow-up: 24 months	The mean change in disability score was –1.72	**MD 0.94 higher** (0.28 lower to 2.17 higher)	—	160 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	Higher scores on the HFMS indicate better function.[a]
Change in muscle strength	Not measured					
Acquiring the ability to stand or walk	Not measured					
Change in quality of life assessed with: PedsQL Neuromuscular Module Score: 0–100 Follow-up: 24 months	—	**MD 0.25** (4.58 lower to 5.08 higher)	—	108 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	Higher scores on the PedsQL indicate a better quality of life. Scores on participants aged > 5 years.
Change in pulmonary function assessed with: FVC (in % predicted) Follow-up: 24 months	The mean change in pulmonary function was +6.16 % predicted	**MD 1.88 % predicted lower** (3.14 lower to 6.91 higher)	—	102 (1 RCT)	⊕⊕⊖⊖ **Low**[b,c]	—

Time from beginning of treatment until death or full-time ventilation Follow-up: 24 months	2 participants died; 1 with cardiac arrest (olesoxime group) and 1 with increased bronchial secretions (placebo group). Deaths were not deemed to be related to treatment.		—	160 (1 RCT)	⊕⊕⊕⊖ **Moderate**[c]	—
Adverse events related to treatment Follow-up: 24 months	1000 per 1000	950 per 1000	**RR 0.95** (0.91 to 0.99)	165 (1 RCT)	⊕⊕⊕⊖ **Moderate**[d]	612 events occurred in 57 participants in the placebo group. 1104 events occurred in 108 participants in the olesoxime group. Adverse events were systematically, prospectively collected at every study visit. Adverse events: (upper) respiratory tract infection, gastroenteritis, influenza, vomiting, abdominal pain, diarrhoea, cough, pyrexia, pain in extremity, scoliosis, arthralgia, fall, headache.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **FVC:** forced vital capacity; **HFMS:** Hammersmith Functional Motor Score; **MD:** mean difference; **MFM:** Motor Function Measure; **MMT:** manual muscle testing; **PedsQL:** Pediatric Quality of Life Inventory; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for indirectness because trial authors combined two different outcome measures (MFM-32 and MFM20) to assess the primary outcome with no correction in analysis.
[b] Downgraded one level for risk of bias because of differences between baseline groups.
[c] Downgraded one level for imprecision because of the small sample size.
[d] Downgraded one level for imprecision because the small sample size was unlikely to have captured uncommon adverse events.

Summary of findings 6. Oral phenylbutyrate compared to placebo for children with SMA type II

Oral phenylbutyrate compared to placebo for children with SMA type II

Patient or population: children with SMA type II
Setting: outpatient clinic
Intervention: oral phenylbutyrate
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with oral phenylbutyrate				
Change in disability score assessed with: Hammersmith Functional Motor Scale (HFMS) Scale: 0–40 Follow-up: 13 weeks		The mean change in disability score was 0.73	**MD 0.13 lower** (0.84 lower to 0.58 higher)	-	90 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the HFMS indicate better function.
Change in muscle strength assessed with: hand-held dynamometer (in Newtons) Follow-up: 13 weeks	Leg megascore	The mean change in muscle strength (leg megascore) was 3.22 N	**MD 1.04 N higher** (2.46 lower to 4.54 higher)	—	70 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Children aged > 5 years had additional assessment of muscle strength by myometry.
	Arm megascore	The mean change in muscle strength (arm megascore) was –0.42 N	**MD 1.98 N higher** (1.67 lower to 5.63 higher)	—	72 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Children aged > 5 years had additional assessment of muscle strength by myometry.
Acquiring the ability to stand or walk		Not measured					
Change in quality of life		Not measured					
Change in pulmonary function assessed with: FVC (% predicted) Follow-up: 13 weeks		The mean change in pulmonary function was –0.01 % predicted	**MD 0.04 % predicted higher** (0.07 lower to 0.15 higher)	—	67 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	Children aged > 5 years had additional assessment of FVC.
Time from beginning of treatment until death or full-time ventilation Follow-up: mean 13 weeks		No deaths were reported. No data available on ventilation.		—	107 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Adverse events related to treatment Follow-up: 13 weeks		994 per 1000	292 per 1000 (118 to 740)	**RR 3.1** (1.25 to 7.84)	107 (1 RCT)	⊕⊕⊕⊖ **Moderate**[c]	5/53 participants had ≥ 1 adverse events in the phenyl-

					butyrate and placebo group. 19/54 participants had ≥ 1 adverse events in the phenylbutyrate group. Adverse events were systematically and prospectively collected at every study visit. Adverse events included rash, drowsiness with hallucinations, nausea and constipation. No full report on types of adverse events was available. 3 participants discontinued the trial because of severe drowsiness, rash or constipation.[b]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **FVC:** forced vital capacity; **HFMS:** Hammersmith Functional Motor Score; **MD:** mean difference; **MFM:** Motor Function Measure; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level because of risk of bias.
[b] Downgraded one level for imprecision because the small sample size.
[c] Downgraded one level because of imprecision on small sample size. Small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 7. Subcutaneous somatotropin compared to placebo for children and adults with SMA types II and III

Subcutaneous somatotropin compared to placebo for children and adults with SMA types II and III

Patient or population: children and adults with SMA types II and III
Setting: outpatient clinic
Intervention: subcutaneous somatotropin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence	Comments

		Risk with placebo	Risk with subcutaneous somatotropin			(GRADE)	
Change in disability score assessed with: HFMSE Scale: 0–66 Follow-up: 3 months		The median change in disability score was –1.05	**Median change 0.25 higher** (1 lower to 2.5 higher)	—	19 (1 cross-over RCT)	⊕⊖⊖⊖ **Very low**[a,b]	Higher scores on the HFMSE indicate better function.
Change in muscle strength assessed with: MMT with hand-held myometry from Citec (in Newtons) Follow-up: 3 months	Upper limbs	The mean change in muscle strength (upper limbs) was 0.30 N	**MD 0.08 N lower** (3.79 lower to 3.95 higher)	—	19 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
	Lower limbs	The mean change in muscle strength (lower limbs) was 0.95 N	**MD 2.23 N higher** (2.19 lower to 6.63 higher)	—	19 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Acquiring the ability to stand or walk		Not measured					
Change in quality of life Follow-up: 40 weeks		The trial report states that the trial found no significant differences in quality of life between the somatotropin-treated group and the placebo group.		—	19 (1 cross-over RCT)	⊕⊖⊖⊖ **Very low**[b,d]	
Change in pulmonary function assessed with: FVC (in litres) Follow-up: 3 months		The mean change in pulmonary function was –0.11 L	**MD 0.22 L higher** (0.02 lower to 0.4 higher)	—	19 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Time from beginning of treatment until death or full-time ventilation Follow-up: mean 40 weeks		No participant died or required full-time ventilation in either group		—	19 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[b,c]	—
Adverse events related to treatment Follow-up: 40 weeks		368 per 1000	578 per 1000 (278 to 1000)	**RR 1.57** (0.78 to 3.17)	19 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[c,e]	23 adverse events occurred, 14 during somatotropin treatment and 9 during placebo treatment. Adverse events were systematically, prospectively collected at every study visit. Adverse events included headache, arthralgia, myalgia, oedema, elevated serum thyroid-stimulating hormone and myalgia.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FVC:** forced vital capacity; **HFMSE:** Hammersmith Functional Motor Score Expanded; **MD:** mean difference; **MFM:** Motor Function Measure; **MMT:** Manual Muscle Testing; **RCT:** randomised controlled trial; **RR:** risk ratio; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels due to risk of bias. HFMSE ranges were not available and because of the potential carry-over effect due to the cross-over design.
[b] Downgraded one level for imprecision because of very small study size.
[c] Downgraded one level because of potential bias from carry-over effects due to the cross-over design.
[d] Downgraded two levels due to risk of bias. The report provided no information about how quality of life was measured and did not provide numerical data. There was a potential carry-over effect due to the cross-over design.
[e] Downgraded for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 8. Intravenous thyrotropin releasing hormone compared to placebo for children with SMA types II and III

Intravenous thyrotropin releasing hormone compared to placebo for children with SMA types II and III

Patient or population: children with SMA types II and III
Setting: in hospital treatment
Intervention: intravenous TRH
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with intravenous TRH				
Change in disability score	Not measured					
Change in muscle strength assessed with: hand-held dynamometry (CSD-500, Amitec; in pounds) Scale: 0–6 Follow-up: 5 weeks	The mean change in muscle strength was 0.48 pounds	**MD 0.34 pounds higher** (0.54 lower to 1.22 higher)	—	9 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Acquiring the ability to stand or walk	Not measured					
Change in quality of life	Not measured					

Change in pulmonary function	Not measured					
Time to death or full-time ventilation	Not measured but no deaths reported		—	9 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Adverse events related to treatment	No events in 3 participants treated with placebo	12 events in 6 participants treated with TRH	—	9 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c,d]	Adverse events included abdominal discomfort, flushing, nausea and vomiting.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **SMA:** spinal muscular atrophy; **TRH:** thyrotropin-releasing hormone.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level for sample size.
[b] Downgraded two levels for baseline imbalance and lack of allocation concealment.
[c] Downgraded one level for imprecision because the small sample size is unlikely to have captured uncommon adverse events.
[d] Downgraded one level for indirectness, because data on adverse events was not collected systematically.

Summary of findings 9. Oral valproic acid plus acetyl-L-carnitine compared to placebo for non-ambulatory children with SMA types II and III

Oral valproic acid + acetyl-L-carnitine compared to placebo for non-ambulatory children with SMA types II and III

Patient or population: non-ambulatory children with SMA types II and III
Setting: outpatient clinic
Intervention: oral valproic acid + acetyl-L-carnitine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with placebo	Risk with oral valproic acid + acetyl-L-carnitine				
Change in disability score assessed with: MHFMS Scale: 0–40 Follow-up: 6 months	The mean change in disability score was 0.18	**MD 0.64 higher** (1.1 lower to 2.38 higher)	—	61 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	Higher scores on the MHFMS indicate better function.
Change in muscle strength assessed with: myometry with myometer (in kg) Follow-up: 6 months	The mean change in muscle strength was –0.25 kg	**MD 1.43 kg higher** (0.69 lower to 3.56 higher)	—	16 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	Only performed in participants aged > 5 years.
Acquiring the ability to stand or walk	Not measured					
Change in quality of life assessed with: PedsQL Scale: 0–100 Follow-up: 6 months	The mean change in quality of life was 0.3	**MD 2.2 lower** (9.27 lower to 4.87 higher)	—	54 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,c,d]	Higher scores on the PedsQL indicate better quality of life. Only 54 participants completed PedsQL at follow-up. Characteristics of this subset are unknown.
Change in pulmonary function assessed with: FVC (in % predicted) Follow-up: 6 months	No numerical data available for analysis		—	24 (1 RCT)	⊕⊕⊖⊖ **Low**[b,e]	Only performed in participants aged > 5 years.
Time from beginning of treatment until death or full-time ventilation Follow-up: 6 months	0 deaths or no need for full-time ventilation		—	61 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—
Adverse events related to treatment Follow-up: 12 months	581 per 1000	755 per 1000 (534 to 1000)	**RR 1.32** (0.92 to 1.89)	61 (1 RCT)	⊕⊕⊕⊖ **Moderate**[f]	18/31 participants in the placebo group had ≥ 1 adverse events. 23/30 participants in the valproic acid + acetyl-L-carnitine group had ≥ 1 adverse events. Adverse events were systematically, prospectively col-

lected at every study visit.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **FVC:** forced vital capacity; **MD:** mean difference; **MHFMS:** Modified Hammersmith Functional Motor Scale; **PedsQL:** Pediatric Quality of Life Inventory; **RCT:** randomised controlled trial; **SMA:** spinal muscular atrophy.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded for imprecision because the small sample size.
[b] Downgraded two levels because of very small sample size, inadequately for optimal information size (OIS). Cut off for OIS was the calculated sample size of the trial.
[c] Downgraded one level due to risk of bias. Only a subset of participants completed PedsQL at follow-up.
[d] Downgraded one level due to inconsistency. Only a subset of participants completed follow-up.
[e] Downgraded one level due to risk of bias. Data on pulmonary function was not available.
[f] Downgraded for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

Summary of findings 10. Oral valproic acid compared to placebo for ambulatory adults with SMA type III

Oral valproic acid compared to placebo for ambulatory adults with SMA type III

Patient or population: ambulatory adults with SMA type III
Setting: outpatient clinic
Intervention: oral valproic acid
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with oral valproic acid				
Change in disability score assessed with: SMAFRS Scale: 0–50 Follow-up: 6 months	The mean change in disability score was –0.35	**MD 0.06 higher** (1.32 lower to 1.44 higher)	—	31 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[a,b]	Higher scores on the SMAFRS indicate better function.

Change in muscle strength assessed with: MVICT (in Newtons) Follow-up: 6 months	Arms	The mean change in muscle strength of arms was –0.01 N	**MD 0.23 N lower** (1.03 lower to 0.57 higher)	—	30 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
	Legs	The mean change in muscle strength of legs was 0.35 N	**MD 0.37 N lower** (1.09 lower to 0.35 higher)	—	30 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[a,b]	—
Acquiring the ability to stand or walk		Not measured					
Change in quality of life assessed with: mini-SIP Scale: 0–19 Follow-up: 6 months		The mean change in quality of life was 0.91	**MD 1.1 lower** (3.8 lower to 1.6 higher)	—	28 (1 cross-over RCT)	⊕⊕⊖⊖ **Moderate**[a]	Higher score on the mini-SIP indicates a poorer health status.
Change in pulmonary function assessed with: FVC (in % predicted) Follow-up: 6 months		The mean change in pulmonary function was 0.53% predicted	**MD 1.24% predicted lower** (4.71 lower to 2.23 higher)	—	24 (1 cross-over RCT)	⊕⊕⊕⊖ **Low**[a,b]	—
Time from beginning of treatment until death or full-time ventilation Follow-up: 6 months		No deaths or full-time ventilation		—	33 (1 cross-over RCT)	⊕⊕⊕⊖ **Low**[a,b]	—
Adverse events related to treatment Follow-up: 12 months		455 per 1000	364 per 1000 (200 to 655)	**RR 0.80** (0.44 to 1.44)	33 (1 cross-over RCT)	⊕⊕⊖⊖ **Low**[a,c]	96 adverse events occurred, 66 in the placebo group and 30 in the valproic acid group. Adverse events were systematically, prospectively collected at every study visit and included upper airway tract infection or symptoms, dizziness, headache, peripheral neuropathy, tremor, fatigue, pain, abdominal pain, nausea, vomiting, decreased platelet count, weight gain and alopecia.[a,b]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **FVC:** forced vital capacity; **MD:** mean difference; **mini-SIP:** mini-Sickness Impact Profile; **MVICT:** maximum voluntary isometric contraction testing; **RCT:** randomised controlled trial; **SMA:** spinal muscular atrophy; **SMAFRS:** Spinal Muscular Atrophy Rating Scale; **TRH:** thyrotropin-releasing hormone.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level because of potential carry-over effect due to the cross-over design.
[b] Downgraded one level for imprecision because of very small study size.
[c] Downgraded for imprecision because the small sample size is unlikely to have captured uncommon adverse events.

BACKGROUND

Description of the condition

Spinal muscular atrophy (SMA) is a neuromuscular disorder of childhood and adolescence with an annual incidence of 1 in 6000 to 1 in 12,000 people (Arkblad 2009; Cobben 2001; Nicole 2002). It is caused by degeneration of anterior horn cells in the spinal cord and characterised by progressive muscle weakness (Iannaccone 2001; Talbot 1999). Other parts of the peripheral nervous system such as the neuromuscular junction (NMJ), and possibly muscles and other organs, may also be affected (Braun 1995; Cifuentes-Diaz 2002; Kariya 2008; Murray 2008).

SMA is an autosomal-recessive disease caused by the homozygous deletion of the *SMN1* gene, which has been mapped to chromosome 5q11.2-13.3 (Brzustowicz 1990; Gilliam 1990; Lefebvre 1995; Melki 1990a; Melki 1990b). The deleted gene results in survival motor neuron (SMN) protein deficiency. Chromosome 5q11.2-13.3 contains the duplicated *SMN1* and *SMN2* genes (Iannaccone 1998; Nicole 2002). The *SMN1* and *SMN2* genes are almost identical, but a crucial C to T nucleotide difference in exon 7 results in the exclusion of exon 7 from most SMN2 messenger ribonucleic acid (mRNA) copies (Lefebvre 1995; Lorson 1999). The functional *SMN1* gene, which is transcribed into full-length mRNA that produces the bulk of stable SMN protein, is lacking in people with SMA. The *SMN2* gene, which is 80% to 90% transcribed into a truncated form lacking exon 7, only produces residual levels of full-length SMN mRNA and protein (Cartegni 2006; Lorson 1999). The clinical severity of the disease is related to the number of copies of the *SMN2* gene (Feldkotter 2002; Harada 2002; Piepers 2008; Swoboda 2005; Wadman 2017).

The cellular functions of the SMN protein are multiple (Sumner 2007), including ribonucleoprotein (RNP) assembly (Burghes 2009; Gendron 1999; Jablonka 2000; Lefebvre 1998; Pellizzoni 1998), motor axon outgrowth and axonal transport (McWhorter 2003; Rossoll 2003), protection against *superoxide dismutase 1* (*SOD1*) toxicity (Zou 2007), endocytosis (Hosseinibarkooie 2016; Riessland 2017), and ubiquitin homeostasis (Wishart 2014).

Muscle weakness in SMA occurs predominantly in the axial and proximal muscle groups, with the lower limbs more affected than the upper limbs (Kroksmark 2001; Thomas 1994). In more severe cases of SMA, intercostal muscles are also weakened, usually with relative sparing of the diaphragm. Survival depends primarily on respiratory function and not necessarily on motor ability (Dubowitz 1995; Russman 1992; Talbot 1999). There is often a fine tremor in the fingers (Iannaccone 1998). Although the face is often spared, tongue fasciculations and facial weakness are not unusual findings (Iannaccone 1993). Cognitive function of people with SMA is normal (Iannaccone 1998; Thomas 1994). Electrophysiological examination shows denervation and reinnervation (Iannaccone 1998; Nicole 2002; Swoboda 2005).

Classification of SMA according to the International SMA Collaboration distinguishes five types (0 to IV), which are based on age of onset and maximal acquired motor function (Finkel 2015; Mercuri 2012; Munsat 1992). SMA types 0, I and IV represent the two ends of the spectrum of SMA, which are outside the scope of this review.

SMA type II is also known as intermediate SMA, juvenile SMA and chronic SMA. The age of onset is between six and 18 months. Children with SMA type II develop the ability to sit independently but are never able to walk without support. They often develop severe pulmonary and orthopaedic complications (Bertini 2005). The children generally survive beyond two years of age and usually live into adolescence or longer (Russman 1996; Zerres 1995; Zerres 1997).

SMA type III is known as Kugelberg-Welander disease, Wohlfart-Kugelberg-Welander disease and mild SMA. The age of onset is after 18 months. Children with SMA type III develop the ability to walk independently at some time, although many lose this ability later in life. Most people with SMA type III have a normal life expectancy (Russman 1992; Zerres 1995; Zerres 1997). SMA type III is often further divided into SMA type IIIa (disease onset before 36 months of age) and SMA type IIIb (disease onset after 36 months of age) (Zerres 1995).

Description of the intervention

Drug treatment to modify the course of SMA types II and III is urgently needed. Management of SMA until recently has consisted of preventing or treating complications of the condition (Iannaccone 1998; Russman 2003; Finkel 2018; Mercuri 2018). Administration of agents capable of increasing the expression of SMN protein levels may improve the outcome in SMA (Feldkotter 2002; Gavrilina 2008; Lorson 1999). Transcriptional SMN2 activation, facilitation or correction of SMN2 splicing, translational activation and stabilisation of the full-length SMN protein are possible therapeutic strategies for SMA. Other strategies are improvement of motor neuron viability by neuroprotective or neurotrophic agents (Lunn 2008; Thurmond 2008; Wirth 2006a). Recently, trials with splice-site-modulators (Chiriboga 2016; EMBRACE 2015; Finkel 2016; Finkel 2017 (ENDEAR); Mercuri 2018 (CHERISH); NCT01703988; NCT02052791; NCT02122952; NCT02268552; SHINE 2015), ribonucleic acid (RNA)-degradation inhibitors (Butchbach 2010; Gogliotti 2013; van Meerbeke 2013), and compounds that replace the *SMN1* gene have started (Appendix 1).

Various drugs that might slow down or cure SMA have been tested in open and (un)controlled studies of people with SMA types II and III, including thyrotropin-releasing hormone (TRH) (Takeuchi 1994; Tzeng 2000), gabapentin (Merlini 2003; Miller 2001), phenylbutyrate (Mercuri 2004; Mercuri 2007; NPTUNE01 2007; STOPSMA 2007), creatine (Wong 2007), valproic acid (Conceicao 2010; JPRN-JapicCTI-163450 2016; Kissel 2014; Kissel 2011; NCT01671384; Saito 2014; SMART01; SMART02; SMART03; Swoboda 2009; Swoboda 2010), hydroxyurea (Chang 2002; Chen 2010; Liang 2008; NCT00568802), somatropin (Kirschner 2014), carnitine (Kissel 2014; Merlini 2007; Swoboda 2010), salbutamol (Giovannetti 2016; Khirani 2017; Kinali 2002; Morandi 2013; Pane 2008; Pasanisi 2014; Prufer de Queiroz Campos Araujo 2010; Tan 2011), riluzole (Abbara 2011; ASIRI 2008; Russman 2003), lamotrigine (Nascimento 2010), celecoxib (NCT02876094), olesoxime (Bertini 2017), *SMN1* gene therapy (Mendell 2016; NCT02122952; Sproule 2016), *SMN2* antisense oligonucleotides (ASO) (Chiriboga 2016; Mercuri 2018 (CHERISH); NCT01703988; NCT02052791; SHINE 2015), small molecules (JEWELFISH 2017; MOONFISH 2014; NCT02644668; SUNFISH 2016), and NMJ-interactors (EMOTAS 2014; NCT01645787; SPACE).

Below we describe the working mechanisms, preclinical studies in SMA models, and results of studies and trials of the various drugs tested in people with SMA type II and III.

It was not clear on clinical grounds whether the patient populations in studies on coenzyme Q10, lithium carbonate and guanidine hydrochloride had a genetically confirmed diagnosis of SMA, partially because *SMN* gene analysis was not possible prior to 1991 (Angelini 1980; Folkers 1995; Il'ina 1980). Therefore, we have not discussed the therapeutic effects of these drugs.

In vitro and animal studies have found several other compounds to have an effect on SMN expression, but they are as yet untested in people with SMA. Therefore, they are outside the scoop of this review. See Appendix 2 for a brief description of these compounds.

SMN1 gene therapies are outside the scope of this review. We have added some information in Appendix 1 for overall completeness.

Antisense oligonucleotides

ASOs or 'morpholinos', are synthetic strands of nucleic acid that are able to interfere with (stimulate or inhibit) mRNA products of the target DNA sequence. In this way, ASOs can modify potential splice sites and interfere with splicing (Porensky 2013). Multiple ASOs for the *SMN2* gene have been developed and investigated (Bogdanik 2015; Keil 2014; Nizzardo 2014; Osman 2014; Shababi 2012; Skordis 2003; Staropoli 2015; Zhou 2013; Zhou 2015). The intronic splice silencer in intron 7 of *SMN2* is called nusinersen (formerly known as SMN Rx 39443, IONIS SMN Rx or ISIS-SMN Rx). This compound specifically targets the splice silencer in intron 7 and ensures the inclusion of *SMN2* exon 7, which results in increased SMN2 full-length mRNA and protein production (Hua 2010). Nusinersen has subsequently demonstrated improved performance and survival in SMA animal models (Hua 2011; Passini 2011). Nusinersen is an intrathecally injected therapy.

Carnitine

L-carnitine, an essential cofactor for the beta-oxidation of long-chain fatty acids, inhibits mitochondrial injury and apoptosis both in vitro and in vivo (Bigini 2002; Bresolin 1984). Acetyl-L-carnitine, the acetylated derivative of L-carnitine, shows neuroprotective and neurotrophic activity in motor neuron cultures (Bigini 2002). L-carnitine treatment restored the level of free carnitine in one animal model of SMA (Bresolin 1984).

Celecoxib

Treatment with celecoxib increased SMN RNA and protein levels in vitro and in models of severe SMA mice by activating the p38 pathway (Farooq 2013), and might have a neuroprotective effect by inhibition of glutamate release (Bezzi 1998). Glutamate is released after presynaptic depolarisation and if not efficiently cleared, leads to increased levels of free radicals, and potentially to degeneration of motor neurons (Bryson 1996).

Creatine

Creatine might have therapeutic benefit by increasing muscle mass and strength through its role as an energy shuttle between mitochondria and working musculature, and is thought to exert neuroprotective effects (Bessman 1981; Ellis 2004; Tarnopolsky 1999).

Gabapentin

Gabapentin has a neuroprotective role by diminishing the excitotoxicity of glutamate (Greensmith 1995; Merlini 2003; Taylor 1998).

Hydroxyurea

Hydroxyurea is a histone deacetylase inhibitor. Studies have suggested a therapeutic role for these agents in SMA, as they appear to activate *SMN2* transcription (Darras 2007; Kernochan 2005; Wirth 2006b). In vitro, hydroxyurea increases *SMN2* gene expression and production of SMN protein in cultured lymphocytes of people with SMA (Grzeschik 2005; Liang 2008).

Lamotrigine

Lamotrigine is a glutamate inhibitor and might prevent motor neuron death (Casanovas 1996).

Olesoxime

The experimental drug olesoxime (TRO19622) is thought to modulate the mitochondrial permeability transition pore (mPTP) opening, which might influence cell apoptosis of, for example, motor neurons (Bordet 2007; Bordet 2010).

Phenylbutyrate

Phenylbutyrate is a histone deacetylase inhibitor. In fibroblast cultures and leukocytes of people with SMA, phenylbutyrate increased SMN transcript expression (Also-Rallo 2011; Andreassi 2004; Brahe 2005).

Valproate

Valproate is another histone deacetylase inhibitor that increases SMN protein in vitro by increasing transcription of *SMN2* gene (Kernochan 2005; Weihl 2006). It also has an antiglutamatergic effect (Kim 2007). Valproate has been tested in various models of SMA and showed positive results on SMN expression in vitro (Brichta 2003; Brichta 2006; Sumner 2003) and in vivo (Piepers 2011).

Salbutamol

Some studies have documented positive effects of oral beta$_2$-adrenoceptor agonists on human skeletal muscle (Caruso 1995; Kindermann 2007; Mack 2014; Martineau 1992). Trials investigating effects of oral beta$_2$-adrenoceptor agonists in people with NMJ disorders have demonstrated improvement of motor function (Burke 2013; Liewluck 2011; Lorenzoni 2013; Rodríguez Cruz 2015). Since abnormal development of the NMJ and dysfunction of neuromuscular synaptic transmission occur in SMA (Braun 1995; Kariya 2008; Kong 2009; Murray 2008; Wadman 2012a), beta^2-adrenoceptor agonists might have an positive effect on muscles and NMJs in SMA. In fibroblasts of people with SMA, salbutamol increases the levels of SMN2 full-length mRNA and the SMN protein (Angelozzi 2008). In 12 people with SMA types II and III who received six months of treatment with oral salbutamol, leukocytes showed a significant and constant increase in SMN2 full-length transcript levels (Tiziano 2010).

Small molecules

RO6885247/RG7800

The small molecule RO6885247/RG7800 selectively modulates *SMN2* splicing towards the inclusion of exon 7 and thereby stimulates production of full-length SMN2 mRNA. Administration of RO6885247/RG7800 improves and almost rescues motor function and survival of SMA mice (Naryshkin 2014).

RO7034067/RG7916

The small molecule RO7034067/RG7916 modulates *SMN2* splicing, but exact details of its structure and pharmacology are not available. One phase I trial with RO7034067/RG7916 combined with itraconazole in healthy volunteers showed a dose-dependent increase of SMN2 mRNA transcripts, but results were only reported in a conference abstract, with further publication of data pending (NCT02633709; Sturm 2016).

CK-2127107

CK-2127107/CK-107 (2-aminoalkyl-5-N-heteroarylpyrimidine) is a small-molecule fast skeletal troponin activator candidate that has been tested in conditions of muscle weakness, fatigue and heart failure (Hwee 2015). It might have a beneficial effect in SMA because of muscle protection, increased muscle strength in skeletal muscle, and delay of onset and extent of muscle fatigue (Andrews 2018). One report of a phase I study in healthy men reported that the drug was well tolerated and there were no serious adverse events (Rudnicki 2016).

Somatropin

Somatropin, also called growth hormone or somatomedin C, is a small polypeptic hormone produced in the pituitary gland. It interacts with growth hormone receptors primarily in the muscles and liver, in which it induces insulin-like growth factor-1 (IGF-1). Because of its primary role in liver and muscle metabolism, IGF-1 seems to play an important role during muscle development and induces muscle regeneration after injury and denervation (Duan 2010). IGF-1 stimulates myoblast and motor neuron proliferation, induces myogenic differentiation and generates myocyte hypertrophy in vitro and in vivo (Bosch-Marcé 2011; Murdocca 2012). In vitro studies of motor neuron tissue cultures of rat spinal cord showed that IGF-1 was one of the neuroprotective hormones that enhanced the survival of motor neurons and reduced their susceptibility to glutamate-induced neurotoxicity (Corse 1999). One study showed that intracerebroventricular injections of IGF-1 next to a SMN trans-splicing RNA vector had a positive effect on disease severity and prolonged survival of severe SMA mice (Shababi 2011). One study showed that overexpression of IGF-1 increased muscle mass, and that administration of a combination of IGF-1 and trichostatin-A improved survival and motor function in SMA mice (Bosch-Marcé 2011). Biondi 2015 showed that underexpression of IGF-1 receptors alone improved the motor function and the life span of SMA mice. Two studies investigated intracerebral injection of AVV-IGF-1 in SMA mice and showed variable results, with slightly improved motor function and survival due to prevention of muscle atrophy and preservation of NMJs (Tsai 2012; Tsai 2014).

Thyrotropin-releasing hormone

The precise mechanism of action of TRH, a tripeptide produced by the hypothalamus, is unknown. It may have a neurotrophic effect on spinal motor neurons (Takeuchi 1994).

Riluzole

Riluzole is thought to have a neuroprotective effect on motor neurons by blocking the presynaptic release of glutamate. In a mouse model of SMA, riluzole attenuated disease progression (Haddad 2003).

Other neurotrophic factors

Other neurotrophic factors have been considered as potential therapies for motor neuron diseases (Apfel 2001). In a mouse model of SMA, cardiotrophin-1 seemed effective in slowing down disease progression (Lesbordes 2003).

Neuromuscular junction interactors

Studies in SMN-deficient mouse models of SMA have uncovered significant abnormalities in the morphology of the NMJ in SMA, in addition to the well-known motor neuron degeneration (Braun 1995; Kariya 2008; Kong 2009; Murray 2008). Additionally, there was abnormal aggregation of acetylcholine receptors at the muscle endplates in people with SMA type I (Arnold 2004). Electrophysiological studies in people with SMA have shown neurophysiological alterations of the NMJ, which may correspond with the symptoms of fatigability (Dunaway 2014; Montes 2013; Wadman 2012a). Drugs such as pyridostigmine and neostigmine, which have an inhibitory effect on acetylcholinesterase, might directly interact with the NMJ and could improve its function. Other potential NMJ interactors are 3-4 diaminopyridine (3-4 DAP) and 4-aminopyridine (4-AP), which are potassium channel blockers that are presumed to prolong repolarisation and to facilitate the generation of the action potential at the NMJ.

Why it is important to do this review

There has been no treatment to slow progression or cure SMA types II or III (Bosboom 2009; Wadman 2012b).

Many studies have explored the effects of various drugs in SMA animal models or in people with SMA. Currently, several drugs and compounds tested in uncontrolled, unblinded and non-randomised settings have shown possible positive effects on the course of SMA through neuroprotection (e.g. cardiotrophin-1, creatine, gabapentin, lamotrigine and riluzole), induction of *SMN2* activity (histone deacetylase inhibitors, e.g. valproic acid, phenylbutyrate and hydroxyurea), improvement of NMJ transmission (e.g. pyridostigmine), modification of SMN2 RNA (ASOs or small molecules, e.g. nusinersen), genetic restoration of the *SMN1* gene using viral vectors, improvement of muscle metabolism and strength (e.g. creatine), and other (unknown) mechanisms (e.g. somatotropin, salbutamol, TRH). Overall, these studies provide conflicting evidence about the effects of these compounds on muscle strength, motor function and survival in SMA.

The number of studies and trials for drug treatment in SMA has expanded rapidly, which has created a need for a clear, thorough and systematic review of these trials and their results. We used Cochrane Systematic Review methods (Higgins 2011), and the

GRADE approach (Atkins 2004), to review all randomised studies and trials on drug treatment in people with SMA types ii and III to analyse the effect of drug treatments on disability, muscle strength, ability to stand or walk, quality of life, time to death or full-time ventilation and adverse events.

This is an update of a review first published in 2009 and first updated in 2012 (Bosboom 2009; Wadman 2012b). Drug treatment for SMA type I is the subject of a separate Cochrane Review (Wadman 2019).

OBJECTIVES

To evaluate if drug treatment is able to slow or arrest the disease progression of SMA types II and III, and to assess if such therapy can be given safely.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised (alternate or other systematic treatment allocation) studies examining the effect of drug treatment designed to slow or arrest disease progression in children or adults with SMA types II and III. Placebo-controlled cross-over studies were also considered to be eligible for inclusion.

Types of participants

Children or adults with SMA types II and III fulfilling the criteria outlined in Table 1.

Types of interventions

Any drug treatment, alone or in combination, designed to slow or arrest the progress of the disease compared to placebo (or sham) treatment, with no restrictions on the route of administration.

Types of outcome measures

We assessed outcome measures within or up to one year after the onset of treatment and compared to baseline. This is a list of the outcomes of interest within whichever studies are included in the review; we did not use outcomes as criteria for including studies.

Primary outcomes

- Change in disability score (e.g. Gross Motor Function Measure (GMFM), Hammersmith Functional Motor Score (HFMS), Motor Function Measure (MFM) and SMA Functional Rating Scale (SMAFRS)) as determined by the original study authors.

Secondary outcomes

- Change in muscle strength (e.g. dynamometry, isometric strength testing, manual muscle testing (MMT) or Medical Research Council (MRC) score).
- Acquiring the ability to stand within one year after the onset of treatment.
- Acquiring the ability to walk or improvement of walking within one year after the onset of treatment.
- Change in quality of life as determined by quality of life scales.
- Change in pulmonary function (forced vital capacity (FVC) as a percentage of FVC predicted for height). This was not stated in the original protocol, but many trials included a measure of pulmonary function or the strength of respiratory muscles.
- Time from beginning of treatment until death or full-time ventilation (a requirement for 16 hours of ventilation out of 24 hours regardless of whether this was with tracheostomy, a tube or mask).
- Adverse events attributable to treatment during the whole study period, separated into severe (requiring or lengthening hospitalisation, life threatening or fatal) and others.

Search methods for identification of studies

Electronic searches

We searched the following databases on 22 October 2018.

- Cochrane Neuromuscular Specialised Register (in the Cochrane Register of Studies (*CRS*); Appendix 3).
- Cochrane Central Register of Studies (CENTRAL) (in the Cochrane Register of Studies Online (*CRSO*); Appendix 4).
- MEDLINE (1991 to October week 43 2018; Appendix 5).
- Embase (1991 to October week 43 2018; Appendix 6).
- ISI Web of Science Conference Proceedings Citation Index (1991 to October 2018; Appendix 7).

We consulted the following registries on 22 October 2018 to identify additional trials that had not yet been published.

- clinical trials registry of the US National Institute of Health (www.clinicaltrials.gov; Appendix 8).
- the WHO international Clinical trials Registry (www.who.int/ictrp/en/; Appendix 9).

Searches were performed from 1991 onwards because at that time genetic analysis of the *SMN1* gene became widely available and could be used to establish the diagnosis of SMA.

Searching other resources

We handsearched the reference lists of relevant cited studies, reviews, meta-analyses, textbooks and conference proceedings to identify additional studies. We invite readers to suggest studies, particularly in other languages, that should be considered for inclusion.

Data collection and analysis

Selection of studies

For this updated review, two review authors (RW and AV) independently checked titles and abstracts obtained from literature searches to identify potentially relevant trials for full review.

We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review.

From the full texts, two review authors (RW and AV) independently selected trials for inclusion that met the selection criteria. The review authors were not blinded to the trial author and source institution. The review authors resolved disagreement by reaching consensus. We presented an adapted PRISMA flowchart of study

selection (Figure 1), and recorded details of excluded studies in the Characteristics of excluded studies table.

Figure 1. Study flow diagram.

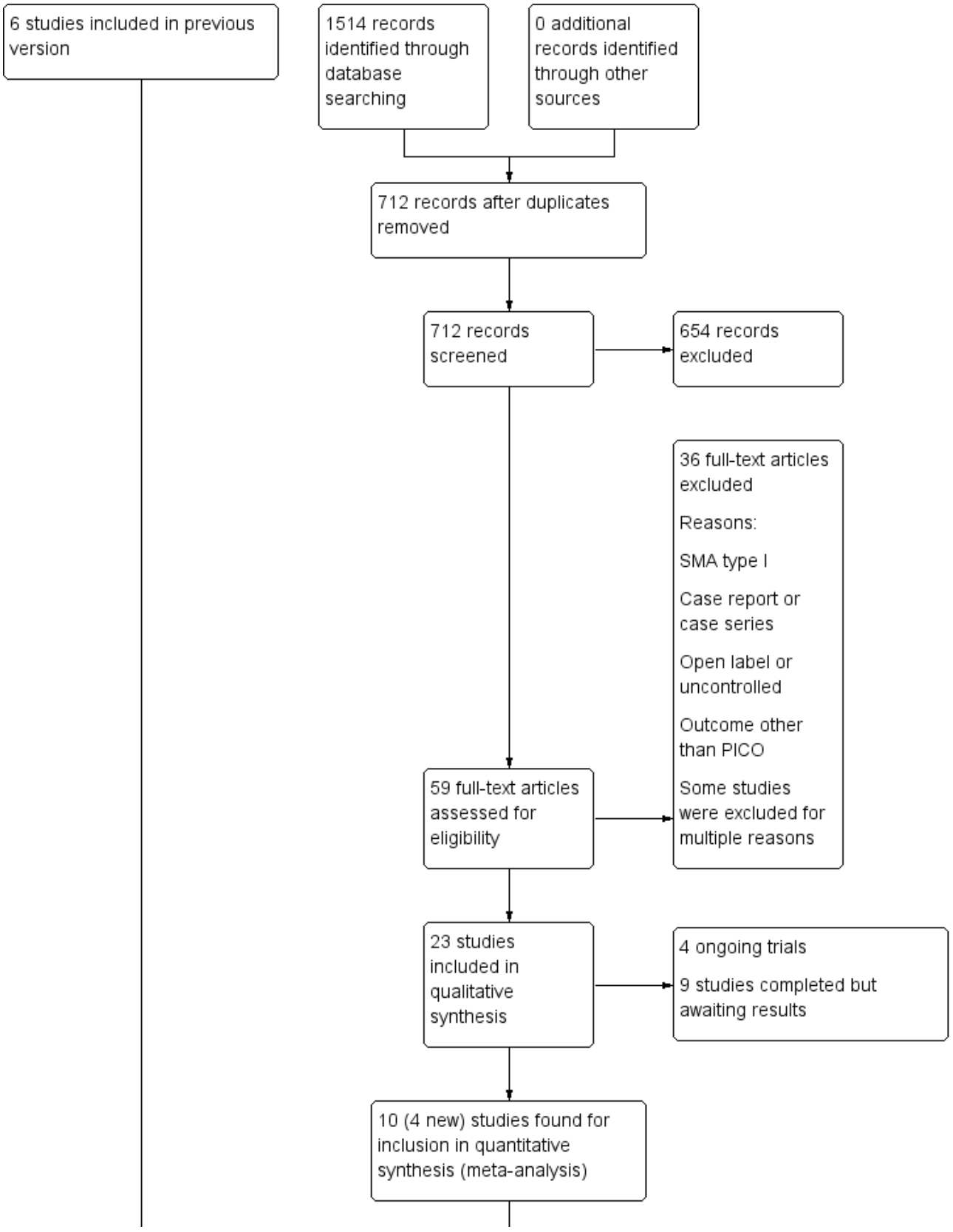
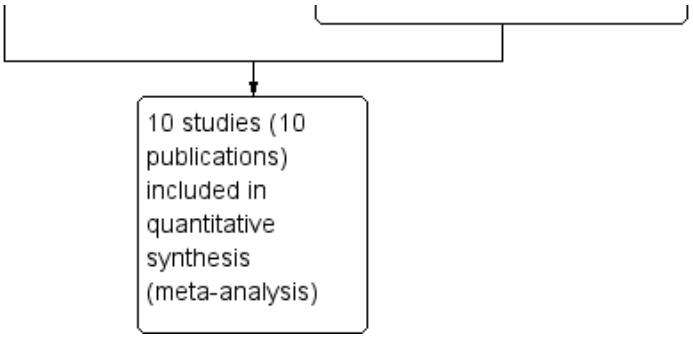


Figure 1. (Continued)



Data extraction and management

Two review authors (RW and AV) independently extracted data using a specially designed data extraction form. We extracted study characteristics from included studies on study design and setting, characteristics of participants (SMA type and age), eligibility criteria, intervention details, the outcomes assessed, source(s) of study funding and any conflicts of interest among investigators and recorded them in the Characteristics of included studies table.

We obtained missing data from the trial authors or pharmaceutical company whenever possible.

Disagreement did not occur, but we would have resolved differences by reaching consensus or with third party adjudication, if necessary.

Assessment of risk of bias in included studies

The 'Risk of bias' assessment took into account allocation concealment, security of randomisation, participant blinding (parent blinding), blinding of outcome assessors, incomplete outcome data (including use of intention-to-treat (ITT) analysis), selective reporting and 'other bias'. We scored each 'Risk of bias' item according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as 'low', 'high' or 'unclear'.

Statistical considerations involved a trade-off between bias and precision. We assessed the risk of bias as 'unclear' when too few details were available to make a judgement of 'high' or 'low' risk, when the risk of bias was genuinely unknown despite sufficient information about the conduct of the study, or when an entry was not relevant to a study. All studies were described by a precise risk of bias.

Two review authors (RW and AV) independently graded the risk of bias in included studies. In the event of disagreement, the review authors reassessed studies and reached agreement by consensus.

Measures of treatment effect

We initially intended to analyse continuous outcomes using mean differences (MDs) with 95% confidence intervals (CIs) in the outcome measures with standard deviation (SD) to quantify the effects of the drug treatment (such as change in disability scores, MRC muscle strength, quality of life) and dichotomous outcomes using a risk ratio (RR) with 95% CIs (such as ability to stand or walk and adverse events). We reported median

For survival or time to full-time ventilation, we would have reported results from Kaplan-Meier survival analyses if data been presented in this way.

Unit of analysis issues

We took into account the level at which randomisation occurred in cross-over trials. We did not anticipate finding cluster-randomised trials and did not anticipate that multiple observations for the same outcome would occur in the included studies.

Where multiple trial arms were reported in a single trial, we would have included only the treatment arms relevant to the review topic. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we would have followed the guidance in Section 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2011). Our preferred approach would have been to perform a multiple-treatments meta-analysis using the indirect comparison method. In case of such analysis in the next update of this review, we will have expert statistical support, as well as subject expertise to analyse the data.

Cross-over trials

If neither carry-over nor period effects were present in cross-over trials and individual participant data or the mean and SD (or standard error) of the participant-specific differences between experimental intervention and control intervention measurements were available, we would have analysed continuous data using a paired t-test in the two-period, two-intervention setting. The effect estimate would have been included in any meta-analysis using the generic inverse variance function in Review Manager 5 (Review Manager 2014). In the absence of data for such an analysis, we would have analysed the treatment and placebo group as if they were parallel groups with the risk of a unit-of-analysis error. In the event of potential carry-over or period effects, we would have analysed data from only the first period.

Dealing with missing data

We carefully evaluated important numerical data, such as the number of screened, randomised participants as well as ITT, as-treated and per protocol populations. We investigated attrition rates (i.e. dropouts, losses to follow-up and withdrawals), and critically appraised issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)). In case of missing outcome data, we would have performed an ITT analysis. If SDs for outcomes were not reported, we would have imputed these values by assuming the SD of the missing outcome to be the mean of

the SDs from studies where this information was reported (Higgins 2011).

Where there were missing data, we contacted the trial investigators, who provided additional data (Kirschner 2014; Kissel 2014; Miller 2001; Wong 2007).

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, we would not have reported study results as the pooled effect estimate in a meta-analysis. We would have identified heterogeneity by visual inspection of the forest plots and by using a standard Chi^2 test with a significance level of alpha = 0.1, in view of the low power of this test.

We would have examined heterogeneity using the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis.

We would have used the approximate guide to interpretation of the I^2 statistic as outlined in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We reviewed and included studies from trial registries to assess the magnitude of publication bias (Appendix 8; Appendix 9). If trials were completed but not yet published, we tried to retrieve results by contacting the principal investigators of the trials.

Data synthesis

We would only have pooled results of studies with the same class of drug treatment.

We would have calculated MDs or RRs with corresponding 95% CI for the pooled data if studies were sufficiently comparable. For continuous outcomes measured using different but comparable scales, we would have calculated standardised mean differences (SMD) and 95% CI, taking care to ensure a consistent direction of effect. If data were not sufficiently comparable between studies, we would have used the standard Review Manager 5 generic inverse variance (GIV) analysis using treatment effect differences with their standard errors.

The review authors estimated differences in medians and CI for the median from participant-level data from Miller 2001 and Wong 2007 using a Hodges-Lehmann estimator.

We would have pooled survival data using the GIV approach. If studies to be pooled had different follow-up periods, we would have used appropriate adjustments, if necessary Poisson regression allowing for the aggregate person-time-at-risk in the study groups.

When Chi^2 analysis showed the data to be heterogeneous, we would have used a random-effects model with a maximum likelihood estimation, carrying out a sensitivity analysis with a fixed-effect model (Mantel-Haenszel RR method). Formal comparisons of intervention effects according to risk of bias would have been done using meta-regression. The major approach to incorporating 'Risk of bias' assessments would have been to incorporate and restrict meta-analyses to studies at low (or lower) risk of bias.

'Summary of findings' tables

We created 'Summary of findings' tables using the following outcomes depending on the outcomes used in the included studies:

- change in disability score (e.g. GMFM, HFMS and MFM);
- change in muscle strength (e.g. dynamometry, isometric strength testing, MMT or MRC;
- acquiring the ability to stand or walk within one year after the onset of treatment;
- change in quality of life as determined by quality of life scales;
- change in pulmonary function (FVC; reported preferably as a percentage of FVC predicted for height or age (or both) or alternatively as total volume in litres);
- time from beginning of treatment until death or full-time ventilation;
- adverse events (reported preferably as number of adverse events or alternatively as number of people with adverse events).

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence (studies that contributed data for the prespecified outcomes). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro GDT software (gradepro.org). We justified all decisions to down- or upgrade the certainty of studies using footnotes and made comments to aid reader's understanding of the review where necessary. Although studies might be graded as high risk in any of the GRADE domains, we would not have excluded the particular study.

Subgroup analysis and investigation of heterogeneity

We would have attempted to determine potential reasons for heterogeneity by examining individual study and subgroup characteristics.

We would have performed subgroup analyses as follows to explore the influence of the following factors (if applicable) on effect sizes:

- SMA type (II versus III);
- SMN2 copy number.

Subgroup analysis based on SMA type and SMN2 copy number is needed, since the subgroups contain a different disease course with potential, significant different effects from or interaction with the intervention.

We would have compared subgroups using the formal tests for subgroup differences in Review Manager 5 (Review Manager 2014).

Sensitivity analysis

We would have performed sensitivity analyses as follows to explore the influence of the following factors (if applicable) on effect sizes. We would have restricted the analysis:

- by taking into account risk of bias;
- to outlier studies (very long, very large, very short or very small) to establish the extent to which they dominated the results.

We would also have tested the robustness of the results by repeating the analysis using different measures of effect size (RR, odds ratios, etc.) and different statistical models (fixed-effect and random-effects models).

Non-randomised evidence

We did not include non-randomised studies in our review. In the Discussion section, we reviewed the results from open and uncontrolled studies.

RESULTS

Description of studies

Results of the search

For this updated review, the numbers of new references found by the searches were: Cochrane Neuromuscular Specialised Register 67 (37 new), CENTRAL 173 (90 new), MEDLINE 676 (351 new), Embase 196 (123 new) and ISI Web of Knowledge 402 (277 new).

Studies with no published data yet, were named by their acronym, or after their trial register code (www.clinicaltrial.gov).

See Figure 1 for a flow diagram of the study selection process.

Included studies

Ten trials fulfilled the selection criteria and remained for inclusion (see Included studies). There were two studies with the same class of drug treatment (valproic acid) (Kissel 2014; Swoboda 2010), but one of these trials used L-carnitine as add-on medication (Swoboda 2010). Two studies only included people with SMA type II (Mercuri 2007; Mercuri 2018 (CHERISH)), one study only included ambulatory people with SMA type III (Kissel 2014), and one study included only non-ambulatory children and adolescents with SMA types II and IIIa (Bertini 2017). Six studies did not make a distinction between the SMA subtypes for inclusion (Chen 2010; Kirschner 2014; Miller 2001; Swoboda 2010; Tzeng 2000; Wong 2007).

Oral creatine versus placebo

Wong 2007 was a double-blind randomised placebo-controlled trial that compared oral creatine with placebo in 55 participants divided into two age groups. Of the 22 participants aged two to five years, 10 received creatine 2 g once a day and 12 received placebo. Of the 33 participants aged five to 18 years, 17 received creatine 5 g once a day and 16 received placebo. Duration of treatment was six months with follow-up at nine months.

Muscle strength for knee extension, knee flexion and elbow flexion were measured bilaterally with the Richmond Quantitative Measurement System. Hand grip strength was measured bilaterally with handheld dynamometry. The best scores were added to obtain a total, upper body and lower body quantitative muscle testing (QMT) score.

Treatment efficacy for each age group was evaluated by ITT analysis of continuous endpoints using analysis of covariance (ANCOVA), which included the qualifying screening measure as the baseline covariate, treatment group as between-subject effect, time as within-subject effect and a subject by time interaction.

The primary endpoint was the change in GMFM from baseline. Secondary endpoints were the changes in muscle strength and pulmonary function tests (e.g. FVC) from baseline in children five to 18 years of age, and change in quality of life (assessed by a neuromuscular module of the parent questionnaire for the Pediatric Quality of Life Inventory (PedsQL)) from baseline. Adverse events were routinely assessed at each visit.

Oral gabapentin versus placebo

Miller 2001 was a double-blind, randomised, placebo-controlled trial that compared oral gabapentin 1200 mg three times a day with placebo in 84 participants at least 21 years old. Duration of treatment was 12 months with follow-up at quarterly intervals while on the treatment.

Muscle strength was measured bilaterally by maximum voluntary isometric contraction (MVIC) of elbow flexion and hand grip. Linear regression analysis was used to determine the change in muscle strength, FVC, SMAFRS and a combined measure of the functional capacity of the lower limbs and quality of life (mini-Sickness Impact Profile: mini-SIP) over time.

Treatment efficacy was determined by comparing the mean percentage change for the treatment and placebo groups in the ITT population (defined as participants with at least two study visits: 37 participants in the treatment group and 39 participants in the placebo group) using the Mann-Whitney test.

The primary endpoint was mean percentage change in muscle strength from baseline. Secondary endpoints were the mean percentage change of FVC, SMAFRS and mini-SIP from baseline, and the occurrence of adverse events. Adverse events were systematically assessed at each visit.

Oral hydroxyurea versus placebo

A phase II/III double-blind randomised placebo-controlled trial compared oral hydroxyurea with placebo in 57 participants with SMA types II and III aged above five years (Chen 2010). Participants received an escalated daily dose over four weeks to a final daily dose of 20 mg/kg/day hydroxyurea or placebo. For the first four weeks, participants received 10 mg/kg/day and for the second four weeks the dose was escalated to 15 mg/kg/day. Duration of treatment was 18 months. Follow-up of post-treatment effects was at six months.

The safety and tolerability of hydroxyurea were measured through serum level measurement. Muscle strength and motor function were measured with the MMT and the GMFM. The GMFM and MMT were performed in all 57 participants. The Modified Hammersmith Functional Motor Scale (MHFMS) was performed in 28 participants with SMA type II and 10 participants with SMA type III who were already non-ambulatory at the beginning of the trial. Lung function was evaluated by FVC measurements. In all participants, quantitative full-length SMN mRNA was measured. Adverse events and serious adverse events were monitored at each assessment by a full blood count, chemistry profiles of liver and renal function, and completion of a questionnaire.

Treatment efficacy was evaluated by ITT analysis with a LOCF approach. Changes in GMFM, MHFMS, MMT, FVC and serum full-length SMN mRNA were analysed by ANCOVA. Measures at time points of the treatment period and the post-treatment period for primary and secondary endpoints were compared by mixed models with adjusted covariates. A two-tailed t-test was used to compare the incidence of adverse events and serious adverse events during the treatment phase.

The primary endpoints were GMFM, MMT and serum full-length SMN mRNA level. Secondary endpoints were the MHFMS and FVC. Adverse events were systematically assessed by a questionnaire at each visit.

Intrathecal nusinersen versus sham procedure

Mercuri 2018 (CHERISH) was a phase III double-blind randomised, sham-procedure controlled study that compared intrathecally injected nusinersen with a sham procedure in 126 participants with SMA type II, aged two to 12 years. Inclusion criteria included a minimal score of 10 and maximum score of 54 on the HMFSE. Participants were randomised 2:1 (nusinersen: sham-procedure) to receive intrathecally injected nusinersen or the sham-procedure. Participants received their treatment or sham-procedure at days one, 29, 85 and 274.

Participants in the treatment group received nusinersen 12 mg intrathecally. The sham-procedure consisted of a small needle prick on the lower back at the location where the lumbar puncture (LP) injection is normally made. The needle would break the skin but no LP injection or needle insertion occurred. The needle prick was covered with the same bandage that was used to cover the LP injection in the treatment group. Treatment period was planned to be 15 months, but was stopped after interim analysis showing beneficiary effects of nusinersen compared to the sham procedure.

Motor abilities were assessed by HFMSE and Upper Limb Module Test (ULMT). Motor milestone development was monitored, including standing and walking with or without support. Assessment of vital signs, weight changes and neurological examination were included. Adverse events and serious adverse events were monitored using laboratory parameters, urine analysis and electrocardiogram.

The interim analysis on treatment efficacy was done by ITT analysis with a LOCF approach and multiple-imputation method to account for missing data. Interim analysis was performed when all the children had been enrolled for at least six months and at least 39 children had completed their 15-month assessment. In the final analysis, the least squares mean changes in the total HFMSE score, the number of World Health Organization motor milestones achieved per child, and the Revised Upper Limb Module (RULM) score and least-squares MDs in change between groups were based on an ANCOVA, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline. The primary endpoint was change from baseline between treatment groups in the HFMSE. Secondary outcome measures were dichotomised analysis of the HFMSE scores (responder analysis of a 3-point change in HFMSE), change from baseline in ULMT, milestone development and adverse events. Adverse events were systematically assessed at each visit.

Oral olesoxime versus placebo

Bertini and colleagues performed a double-blind, randomised, placebo-controlled trial compared oral olesoxime with placebo in 165 non-ambulatory participants with SMA types II and IIIa aged three to 25 years (Bertini 2017). Participants were randomised 2:1 (olesoxime:placebo) to receive oral liquid suspension of olesoxime 10 mg/kg once daily or oral liquid suspension of placebo. Treatment period was 24 months.

Participants started with a screening and baseline visit. Follow-up visits were scheduled four and 13 weeks after baseline, with follow-up every 13 weeks during the treatment period of 24 months.

Motor abilities were assessed by MFM at weeks 26, 52, 78 and 104, and the HMFS at weeks 13, 39, 65, 91 and 104. Children younger aged younger than six years (n = 48) were assessed with the adapted version of the MFM-32, the MFM-20, where participants older than six years (n = 112) were tested with the MFM-32. Electromyography, including compound muscle action potential (CMAP) and motor unit number estimation (MUNE) assessments of ulnar and hypothenar nerves, were performed at weeks 26, 52, 78 and 104. FVC was tested at weeks 13, 26, 39, 52, 78 and 104. The PedsQL was tested every visit. Clinical examination and electrocardiogram were performed every visit as well. Safety laboratory studies were performed at baseline and every consecutive visit. Serum levels of olesoxime were reviewed at weeks four, 13 and 52.

Data analysis was done with ITT analyses using mixed-effects repeated measure model. An interim analysis was performed at 12 months with predefined criteria to assess whether the trial should be continued or terminated.

The primary endpoint was the change from baseline between treatment groups in MFM, parts D1+D2. Secondary outcome measures were responder analyses of change from baseline in total MFM scores and individual MFM domains and change from baseline in HFMS, CMAP amplitude, MUNE, Clinical Global Impression, FVC and PedsQL. Adverse events were systematically assessed at each visit.

Oral phenylbutyrate versus placebo

Mercuri 2007 was a phase II, double-blind, randomised, placebo-controlled trial that compared oral phenylbutyrate 500 mg/kg/day, divided into five doses and using an intermittent schedule (seven days on treatment, seven days off treatment), with placebo in 107 participants with SMA type II. Duration of treatment was 13 weeks with follow-up at the end of the study period (also at 13 weeks).

Motor function was assessed in all participants. In addition, muscle strength and FVC were assessed in children older than five years. Muscle strength was measured by handheld dynamometry of elbow flexion, hand grip, 3-point pinch, knee flexion and knee extension; the best scores were added to obtain an arm megascore and a leg megascore.

Treatment efficacy was evaluated by ITT analysis in 90 participants (45 in the treatment group and 45 in the placebo group) with continuous endpoints at five and 13 weeks' follow-up using ANCOVA which included the baseline outcome values as covariates, treatment group and age as between-patient factors, time as a

within-patient factor, and possible interaction between treatment group, time and age.

The primary endpoint was the change in HFMS from baseline. Secondary endpoints were the change in muscle strength and FVC from baseline and the occurrence of adverse events. Adverse events were systematically assessed at each visit by means of a questionnaire.

Subcutaneous somatotropin versus placebo

A double-blind, randomised, placebo-controlled, cross-over pilot trial compared subcutaneous injections of somatropin with subcutaneous injections of placebo in 20 participants with SMA types II and III aged between six and 36 years old (Kirschner 2014). Participants were randomised to two cohorts, in which one started with treatment for 12 weeks and crossed over to placebo for 12 weeks after a washout period of eight weeks, while the other cohort started with placebo for 12 weeks and crossed over to treatment for 12 weeks after a washout period of eight weeks. During the 12-week period, participants received either somatotropin 0.015 mg/kg/day subcutaneously in the first week which was increased after one week up to 0.03 mg/kg/day for weeks two to 12 or placebo at the same dose regimen. Duration of the trial was 40 weeks. Follow-up after the last treatment was eight weeks.

Muscle strength was measured with MVIC using hand-held myometry and MRC scale in elbow flexion, handgrip, knee flexion and knee extension at baseline and weeks four, 12, 20, 24 and 32. Motor function was evaluated with the HFMSE, 10-metre walking time and Gowers' time at baseline and weeks four, 12, 20, 24 and 32. Pulmonary functioning test were assessed with FVC and peak cough flow at baseline and weeks 12, 20 and 32. Laboratory studies included IGF-1 serum concentrations and endocrinological measurements at baseline and weeks four, 12, 20, 24, 32 and 40.

Data analysis was done with a modified ITT concept using t-test and Wilcoxon test.

The primary endpoint was change in quantitative muscle strength of upper limb using hand-held myometry in elbow flexion and handgrip. Secondary outcomes measures were change in quantitative muscle strength of lower limb, muscle strength with MMT in seven muscles, change in HFMSE, change in Gowers' time, change in qualitative Gowers' manoeuvre, change in FVC and peak cough flow, and adverse events. Adverse events were systematically assessed at each visit.

Intravenous thyrotropin-releasing hormone versus placebo

Tzeng 2000 was a double-blind, randomised, placebo-controlled trial that compared intravenous TRH 0.1 mg/kg once a day with placebo. Six participants were treated with TRH and three received placebo. The duration of treatment was 29 days over a 34-day period with follow-up and conclusion of the study at five weeks.

Muscle strength was evaluated by dynamometry of the deltoids, biceps, triceps, wrist extensors, hand grip, hip flexors, quadriceps and hamstrings.

Comparisons of total mean muscle strength and electrodiagnostic measures at baseline and at the end of the five-week study period were made using paired t-tests.

The primary endpoint was the change in total mean muscle strength from baseline. Secondary endpoints were change in electrodiagnostic measures and the occurrence of adverse events related to the treatment. Adverse events were collected when spontaneous reported by the participants.

Oral valproic acid (valproate) plus acetyl-L-carnitine versus placebo

One double-blind, placebo-controlled trial compared combination therapy with oral valproic acid and acetyl-L-carnitine to placebo in 61 non-ambulatory children aged between two and eight years (Swoboda 2010). Thirty-one children received treatment with valproic acid 125 mg, given in divided doses two to three times a day and sufficient to maintain overnight trough levels of 100 mg/dL, and acetyl-L-carnitine doses at 50 mg/kg/day divided into two daily doses. Thirty children received a double placebo. The duration of treatment was 12 months in the active treatment arm and six months in the placebo. After six months the placebo group switched over to active treatment per protocol.

In all participants, the MHFMS and GMFM were used to measure functional motor ability at baseline, three, six and 12 months after the start of treatment. The degree of innervation by the ulnar nerve was estimated using maximum ulnar CMAP amplitude. Myometry measurements were performed in children aged five years and older (24 children) with no significant contractures: three times for right and left elbow flexion and for right and left knee extension. Also in the children aged five years and older, pulmonary function testing was performed, which included FVC, forced expiratory volume (FEV), and maximum inspiratory and expiratory pressures (MIP and MEP). Quality of life was assessed using the PedsQL, filled in by parents at each visit. Children aged five years or older completed the age-appropriate PedsQL. Bone mineral density and bone mineral content were measured with dual-energy X-ray absorptiometry (DEXA).

All analyses were performed on an ITT population of 61 people that was defined as all participants randomised to receive study medication. The analysis of variance (ANOVA) test was used to compare treatment groups for change in MHFMS from the baseline data. Non-normally distributed data were tested with the Wilcoxon rank sum test.

The primary endpoints were laboratory safety data, adverse event data and change in MHFMS from baseline after six months. Secondary endpoints included measurement from baseline at six and 12 months in MHFMS, estimates of CMAPs, DEXA, body composition and bone density, quantitative SMN mRNA and quality of life. Adverse events were systematically assessed at each visit.

Oral valproic acid (valproate) versus placebo

Kissel 2014, a double-blind, placebo-controlled, cross-over trial, compared oral valproic acid with placebo in 33 ambulatory participants with SMA type III aged above 18 years old. Participants were divided over two cohorts. Cohort one (16 participants) was first treated with oral valproic acid 10 mg/kg/day to 20 mg/kg/day divided over two or three doses (doses depending on serum levels of valproic acid with preferred levels of 50 mg/dL) for six months, after this period this cohort switched to equal dosage of oral placebo for six months. Cohort two (17 participants) started with six months' treatment with placebo and afterwards crossed over to oral valproic acid 10 mg/kg/day to 20 mg/kg/day divided

over two to three doses (doses depending on serum levels of valproic acid with preferred levels of 50 mg/dL) for six months. Total duration of the trial was 12 months.

Participants started with two baseline visits within a six-week period to assure that the methodologies were reliable and to assure test–retest stability. Clinical assessments were done at three, six and 12 months. Motor abilities were assessed by maximum voluntary isometric contraction testing (MVICT) in bilateral elbow flexors, elbow extensors, knee flexors, knee extensors and grip. Functional motor abilities were tested with modified SMAFRS, the ability to climb four standard stairs and endurance during the six-minute walk test. Muscle mass was measured by DEXA scanning. The degree of innervation by the ulnar nerve was estimated using maximum ulnar CMAP. Pulmonary function testing was performed, which included FVC, FEV and MIP. Quality of life was assessed using the mini-SIP. Safety laboratory studies (chemistry profile, blood and platelet count, transaminases, carnitine profile, amylase, lipase, valproic acid levels) were performed at baseline, two to three weeks after initiation, at thee, six and 12 months and one additional time between six and 12 months. Serum levels of SMN protein and mRNA were performed.

The two baseline visits and the visit closest to the start of the treatment were used as baseline evaluation. Changes from baseline between treatment and placebo at six months were analysed with t-tests and at 12 months with mixed-effects models.

The primary endpoint was the change in MVICT at six months. Secondary outcomes included laboratory safety data, adverse event and change in muscle scores of upper and lower extremities, SMAFRS, CMAPs of the ulnar nerve, DEXA, muscle mass, pulmonary functioning tests, SMN protein levels and mRNA levels from baseline after six and 12 months. Adverse events were systematically assessed at each visit.

Funding

In three trials, pharmaceutical companies were involved in funding, analysis, reporting of results, or a combination of these (Bertini 2017; Kirschner 2014; Mercuri 2018 (CHERISH)). In six trials, pharmaceutical companies provided the study drug without cost and they had no involvement in study design, or analysis and reporting of results (Kissel 2014; Mercuri 2007; Miller 2001; Swoboda 2010; Tzeng 2000; Wong 2007). Authors of one trial were reported to have a patent on the study drug (Chen 2010).

Excluded studies

We identified and assessed 59 studies (36 new) for possible inclusion in the review. We excluded 36 studies (see Characteristics of excluded studies table) because they were not randomised or were uncontrolled (Abbara 2011; Brahe 2005; Brichta 2006; Chang 2002; Chiriboga 2016; Darbar 2011; EMOTAS 2014; Folkers 1995; Giovannetti 2016; JEWELFISH 2017; JPRN-JapicCTI-163450 2016; Kato 2009; Khirani 2017; Kinali 2002; Kissel 2011; Liang 2008; NCT02876094; Mercuri 2004; Merlini 2003; Nascimento 2010; NCT01703988; NCT02052791; NCT03709784; NPTUNE01 2007; OLEOS; Pane 2008; Piepers 2011; Prufer de Queiroz Campos Araujo 2010; Saito 2014; SHINE 2015; SMART01; SMART03; Swoboda 2009; Tan 2011; Tsai 2007; Weihl 2006). We could exclude 13 unpublished studies because they were not randomised or were uncontrolled, with eight of these studies still being ongoing (EMOTAS 2014; JEWELFISH 2017; JPRN-JapicCTI-163450 2016; NCT02876094; NCT03709784; OLEOS; SHINE 2015; SMART03), and five studies being completed but not yet published at time of the search (NCT01703988; NCT02052791; NPTUNE01 2007; Prufer de Queiroz Campos Araujo 2010; SMART01).

Studies awaiting classification

Nine trials were completed but no data were available for analysis (ASIRI 2008; CHICTR-TRC-10001093; Merlini 2007; MOONFISH 2014; Morandi 2013; NCT00568802; NCT01645787; NCT02644668; SPACE) (see Characteristics of studies awaiting classification table). Results of two trials, the EUROsmart trial with acetyl-L-carnitine (Merlini 2007), and a trial with salbutamol (Morandi 2013), were only published in conference abstracts which did not include enough data for analysis (Merlini 2010; Morandi 2013). We also could not obtain the results of three completed randomised, placebo-controlled trials with hydroxyurea (NCT00568802), with riluzole in SMA types II and III (ASIRI 2008), and with 4AP in adults with SMA type III (NCT01645787). One trial was terminated for safety reasons and results are not yet published (MOONFISH 2014). We tried to obtain data and preliminary results for all of these completed but unpublished trials, but data were not available upon request at time of writing.

We could not obtain information about the trial methods or results of the completed two-armed trial on rat nerve growth factor and, therefore, this study is awaiting classification (CHICTR-TRC-10001093).

Ongoing studies

Four trials were ongoing at the time of this search (EMBRACE 2015; NCT01671384; SMART02; SUNFISH 2016) (see Characteristics of ongoing studies table).

Risk of bias in included studies

The 'Risk of bias' assessments for the 10 included trials are shown in the Characteristics of included studies table and summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all 10 included studies.

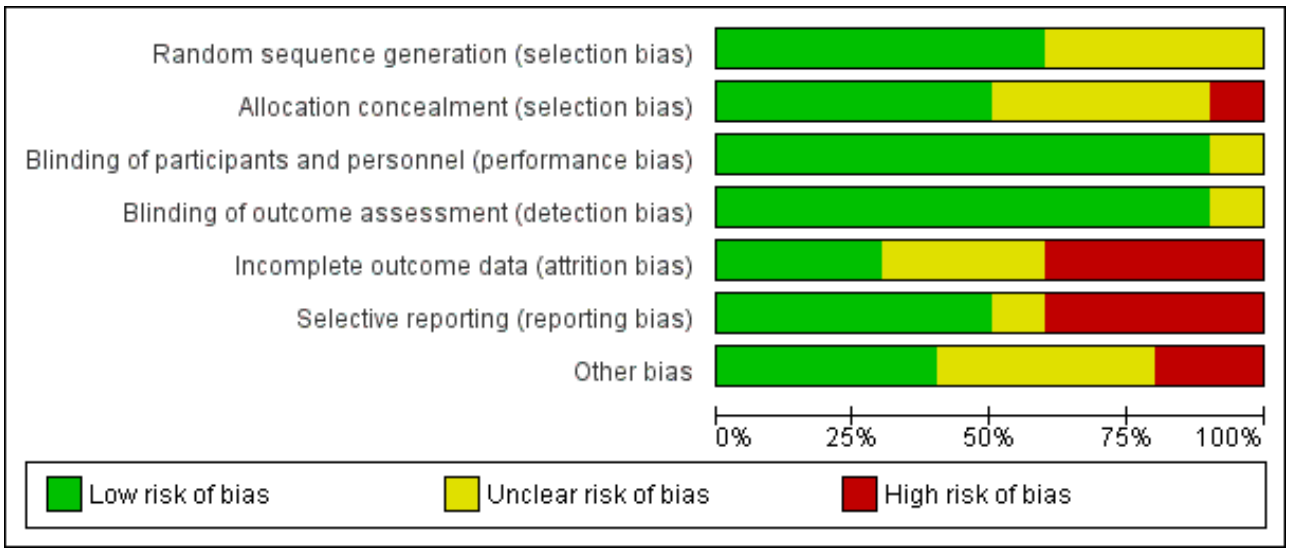
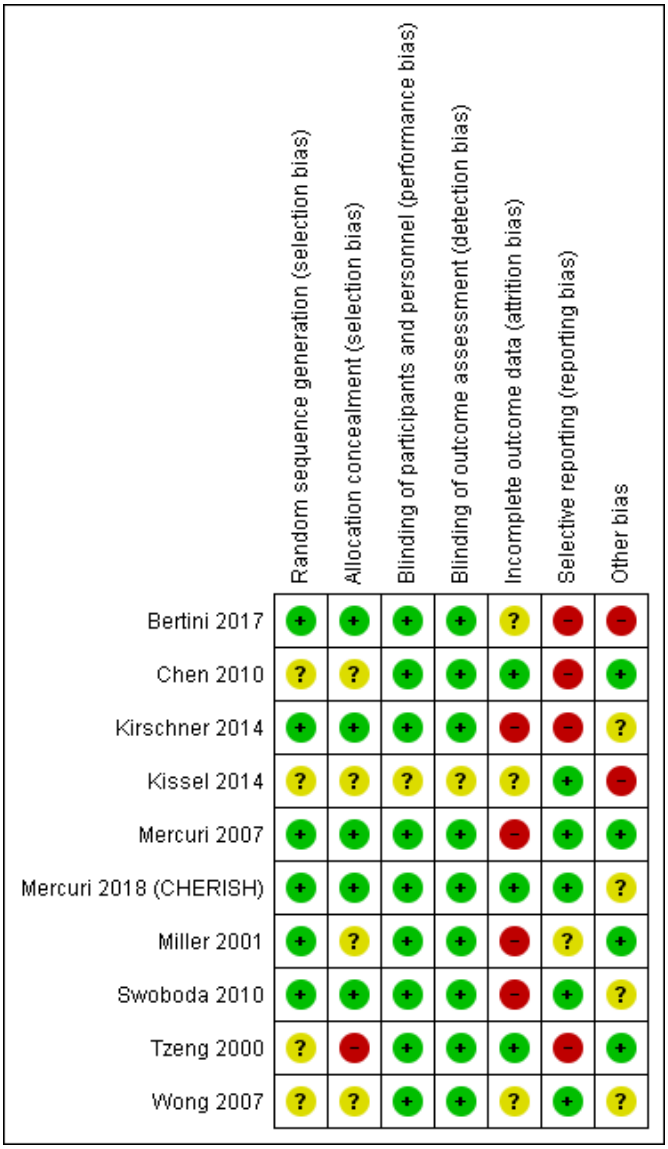


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The randomisation method was not clear in four trials (Chen 2010; Kissel 2014; Tzeng 2000; Wong 2007), but was at low risk of bias in the remaining six trials. Allocation concealment was not clear in four trials (Chen 2010; Kissel 2014; Miller 2001; Wong 2007), but adequately reported in five trials, which we judged at low risk of bias (Bertini 2017; Kirschner 2014; Mercuri 2007; Mercuri 2018 (CHERISH); Swoboda 2010). Allocation concealment was at high risk of bias in one trial (Tzeng 2000), which used a coin toss method. In one trial, there were baseline differences probably due to inadequate randomisation, since muscle strength in the cohort of children aged five to 18 years in the creatine treatment group was slightly weaker than in the placebo group (Wong 2007).

Blinding

Blinding of parents, participants and observers were adequate and at low risk of bias in all trials except Kissel 2014, for which the risk of bias related to blinding was unclear.

Incomplete outcome data

Four trials were at high risk of bias from attrition and three at unclear risk of bias. The method for modified ITT analysis was unknown in Kirschner 2014 and we assessed this trial at high risk of bias. In one trial, the risk of attrition bias was high because fewer than expected numbers of participants provided data for some outcome measures (Swoboda 2010). A difference in the number of children over five years of age providing data on myometry and FVC was unexplained, with data on adverse events limited in Mercuri 2007. This resulted in a high-risk assessment. Follow-up was below 80% in two trials (Miller 2001; Wong 2007). Miller 2001 performed an ITT analysis but participants withdrew for unknown reasons and the number analysed was not the number initially included. We judged the risk of bias in Miller 2001 to be high and in Wong 2007 to be unclear. Participants withdrew for unknown reasons in two other studies; however, ITT analysis possibly minimised the risk of bias, which we judged unclear (Bertini 2017: n = 17; Kissel 2014: n = 4).

Risk of attrition bias in the other trials was low (Chen 2010; Mercuri 2018 (CHERISH); Tzeng 2000).

Selective reporting

Primary outcome measures were adequately stated in all trials. Trial authors provided data to complete analysis of primary and secondary outcomes, including muscle strength (Kirschner 2014; Kissel 2014; Miller 2001; Wong 2007), disability scores (Kirschner 2014; Kissel 2014; Miller 2001; Wong 2007), pulmonary function (Kirschner 2014; Kissel 2014; Wong 2007), quality of life (Kissel 2014; Miller 2001; Wong 2007), and adverse events (Kissel 2014; Miller 2001; Wong 2007).

We assessed four trials at high risk of reporting bias. Two studies dichotomised data post hoc for analysis (Bertini 2017; Chen 2010). A third study measured quality of life but the reporting was incomplete (Kirschner 2014). We also judged Tzeng 2000 at high risk of reporting bias. Although all outcomes were reported, the statistical plan was limited and unclear. Miller 2001 was at unclear risk of bias, as adverse events were not reported. We judged the other five trials at low risk of selective reporting (Kissel 2014; Mercuri 2007; Mercuri 2018 (CHERISH); Swoboda 2010; Wong 2007),

Other potential sources of bias

Two studies were at high risk from other potential sources of bias (Bertini 2017; Kissel 2014) and four at unclear risk (Kirschner 2014; Mercuri 2018 (CHERISH); Swoboda 2010; Wong 2007).

The cross-over design with potential carry-over effects placed two studies at unclear risk of bias (Kirschner 2014; Swoboda 2010) and one study at high risk of bias (Kissel 2014).

In four trials, there were baseline differences, with other potential bias graded as unclear (Mercuri 2018 (CHERISH); Swoboda 2010; Wong 2007) or high (Bertini 2017). In Swoboda 2010, there were baseline differences in gender as the valproic acid plus acetyl-L-carnitine treatment group consisted of 36.6% females compared to 56% females in the placebo group, and there were differences in body mass index. In Mercuri 2018 (CHERISH), we judged the risk as unclear, since the baseline differences resulted in more severely affected children in the nusinersen-treated group. However, there was a beneficial significant effect on motor function in the nusinersen group, the effects of nusinersen even being underestimated in more severely affected children. No definite conclusions on this subject could be drawn. In Bertini 2017, we judged the risk of bias as high because there were differences in mean and median ages between the olesoxime and placebo group, with a higher mean and median age in the placebo group, and the proportion of males and females was uneven between the two treatment groups.

Four trials were at low risk of other potential sources of bias (Chen 2010; Mercuri 2007; Miller 2001; Tzeng 2000).

Effects of interventions

See: **Summary of findings for the main comparison** Oral creatine compared to placebo for children with SMA types II and III; **Summary of findings 2** Oral gabapentin compared to placebo for adults with SMA types II and III; **Summary of findings 3** Oral hydroxyurea compared to placebo for children and adults with SMA types II and III; **Summary of findings 4** Intrathecal injected nusinersen compared to sham procedure for children with SMA type II; **Summary of findings 5** Oral olesoxime compared to placebo for non-ambulatory children and adolescents with SMA types II and III; **Summary of findings 6** Oral phenylbutyrate compared to placebo for children with SMA type II; **Summary of findings 7** Subcutaneous somatotropin compared to placebo for children and adults with SMA types II and III; **Summary of findings 8** Intravenous thyrotropin releasing hormone compared to placebo for children with SMA types II and III; **Summary of findings 9** Oral valproic acid plus acetyl-L-carnitine compared to placebo for non-ambulatory children with SMA types II and III; **Summary of findings 10** Oral valproic acid compared to placebo for ambulatory adults with SMA type III

Meta-analysis was not possible due to the extensive variation in the drug treatments, outcomes and outcome measures, analyses, follow-ups, study designs and the reporting of results in the 10 studies included in the review. We present the detailed results of each trial in tables (Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11).

We re-analysed the data from four trials according to our predefined primary and secondary outcome measures (Kissel 2014; Miller 2001; Tzeng 2000; Wong 2007). To enable this analysis, we obtained the raw study data from the principal investigators of two studies (Miller 2001; Wong 2007). We performed additional analysis on the available data of one study to retrieve MDs and CIs of data (Kissel 2014). We obtained additional data for one study to complete information on effect sizes and CIs (Kirschner 2014). The results of this re-analysis are shown separately for each included trial in Table 2, Table 3, Table 8, Table 9, and Table 11.

Oral creatine versus placebo

Wong 2007 compared creatine versus placebo and reported outcomes at nine months. See Table 2 for numerical results and Summary of findings for the main comparison.

Primary outcome

Change in disability score

Change in disability, assessed by the GMFM was a primary outcome in Wong 2007. Trial authors supplied additional data on GMFM for re-analysis. The change in disability scores showed little or no difference between the treatment and placebo groups (n = 40; moderate-certainty evidence, downgraded one level for imprecision owing to a small sample size).

Secondary outcomes

Change in muscle strength

The study measured muscle strength via quantitative myometry, but (re-)analysis of data showed no evidence of a difference for change in hand, arm, feet, leg or total muscle strength between the treatment and placebo groups (n = 22; low-certainty evidence, downgraded one level for imprecision owing to a small sample size and one level for inconsistency due to unknown cohort representation).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

The study measured quality of life using the mini-SIP and PedsQL. There was no evidence of a difference in quality of life measures between the treatment and placebo groups (n = 38; low-certainty evidence, downgraded one level for imprecision owing to a small sample size and one level for inconsistency).

Change in pulmonary function

The study measured change in FVC in participants more than five years old. There was no evidence of a difference in pulmonary function between the treatment and placebo groups (n = 23; low-certainty evidence, downgraded one level for imprecision owing to a small sample size and one level for inconsistency due to unknown cohort representation).

Time from beginning of treatment until death or full-time ventilation

One participant in Wong 2007 died. The death was reported not to be related to the study treatment and occurred in the placebo group. None of the participants reached the state of more than 16 hours' ventilation a day (n = 40; moderate-certainty evidence, downgraded one level for imprecision owing to a small sample size).

Adverse events, separated into severe and others

In Wong 2007, adverse events rates were similar in the creatine and placebo groups: 13/27 participants who received creatine and 16/28 participants who received placebo had an adverse event (n = 40; low-certainty evidence, downgraded two levels for study limitations (risk of bias) and because it is unlikely the trial captured uncommon adverse events (risk of imprecision). The report did not include information on type of adverse events. Data on the number of adverse events were available for analysis, but the trial authors were unable to provide other data on (severe) adverse events on request.

Oral gabapentin versus placebo

Miller 2001 compared gabapentin versus placebo and reported outcomes at 12 months. See Table 3 for numerical results and Summary of findings 2.

Primary outcome

Change in disability score

Change in disability, measured with the SMAFRS, was a primary outcome in Miller 2001.

There was no evidence of a difference for change in disability scores between the treatment and placebo groups (n = 66; low-certainty evidence, downgraded two levels for study limitations (risk of bias and imprecision)).

Secondary outcomes

Change in muscle strength

The trial measured muscle strength using quantitative myometry. There was no evidence of a difference for change in hand, arm, feet, leg or total muscle strength between the treatment and placebo groups.

In Miller 2001, some participants were unable to perform all of the muscle strength tests and, therefore, these were not included in the analyses. Moreover, the raw data from this trial showed several extreme values of muscle strength in one particular participating centre. Therefore, we re-analysed the data with and without these outliers, but this did not result in a different statistical outcome. For a limited number of participants in this trial, data were available at 12 months' follow-up. Re-analysis of these limited data also showed no clinically or statistically significant difference for change in muscle strength between the treatment and placebo groups (for total muscle strength, n = 50; low-certainty evidence, downgraded one level for study limitations (risk of bias) and one level for imprecision; Table 3).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

In Miller 2001, none of the participants who were unable to walk before treatment acquired this ability after treatment, and none of the participants who could walk lost this ability in either the treatment or placebo group (n = 73; low-certainty evidence, downgraded one level for study limitations (risk of bias) and one level for imprecision).

Change in quality of life

Quality of life was measured with the use of mini-SIP. There was no evidence of a difference in quality of life between the treatment and placebo groups (n = 73; low-certainty evidence, downgraded one level for study limitations (risk of bias) and one level for imprecision).

Change in pulmonary function

Miller 2001 included only adults and measured the change in FVC. There was no evidence of a difference in pulmonary function between the treatment and placebo groups (n = 65; low-certainty evidence, downgraded one level for study limitations (risk of bias) and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 84; moderate-certainty evidence, downgraded one level for imprecision).

Adverse events, separated into severe and others

Miller 2001 did not provide specific information on adverse events (n = 65; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Oral hydroxyurea versus placebo

Chen 2010 compared oral hydroxyurea versus placebo, with a follow-up of 18 months. See Table 4 for numerical results. and Summary of findings 3.

Primary outcome

Change in disability score

Chen 2010 measured change in disability as a primary outcome using the GMFM. There was no evidence of a difference in change from baseline between the treatment and placebo groups (n = 57; low-certainty evidence, downgraded two levels for imprecision (wide CIs and small sample size)). The trial also measured the MHFMS in non-ambulatory participants as a secondary outcome. There were no clinically or statistically significant difference between the hydroxyurea and placebo groups (n = 38; moderate-certainty evidence, downgraded one level for imprecision).

Secondary outcomes

Change in muscle strength

Muscle strength was measured via quantitative myometry. There was no evidence of a difference for change in hand, arm, feet, leg or total muscle strength between the treatment and placebo groups (n = 57; moderate-certainty evidence, downgraded one level for imprecision).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

The study did not measure quality of life.

Change in pulmonary function

Chen 2010 measured change in FVC in participants more than five years old. There was no evidence of a difference in pulmonary function between the treatment and placebo groups (n = 57; low-certainty evidence, downgraded one level for indirectness and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

One participant in the treatment group died. The death was reported not to be related to the study treatment. No other deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 57; moderate-certainty evidence, downgraded one level for imprecision).

Adverse events, separated into severe and others

In Chen 2010, all participants had at least one adverse event (n = 57; moderate-certainty evidence, downgraded one level for imprecision) and 19/61 participants had a severe adverse event.

Intrathecal nusinersen versus sham procedure

Mercuri 2018 (CHERISH) compared intrathecal nusinersen versus placebo. Results were reported after 15 months of treatment. See Table 5 for numerical results and Summary of findings 4.

Primary outcome

Change in disability score

Change in disability measured using the HFMSE was a primary outcome in Mercuri 2018 (CHERISH). There were significant differences in HFMSE score in favour of the nusinersen-treated participants compared to the sham procedure-treated participants (n = 126; moderate-certainty evidence, downgraded one level for imprecision). More participants in the nusinersen-treated group than the sham procedure-treated group had a 3-point change in disability score (n = 126; moderate-certainty evidence, downgraded one level for imprecision).

Secondary outcomes

Change in muscle strength

Mercuri 2018 (CHERISH) did not report change in muscle strength.

Acquiring the ability to stand within one year after the onset of treatment

One child treated with nusinersen and one child treated with the sham procedure acquired the ability to stand alone (n = 126; low-certainty evidence, downgraded two levels for imprecision).

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

One child treated with nusinersen acquired the ability to walk with assistance compared to no children in the sham-controlled group (n = 126; low-certainty evidence, downgraded two levels for imprecision).

Change in quality of life

The study did not measure quality of life.

Change in pulmonary function

The study did not measure pulmonary function.

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 126; moderate-certainty evidence).

Adverse events, separated into severe and others

In Mercuri 2018 (CHERISH), 78/84 (93%) participants treated with nusinersen experienced an adverse event, while 42/42 (100%) participants treated with the sham procedure had any adverse event (n = 126; moderate-certainty evidence, downgraded one level for imprecision). Serious adverse events were reported in 14/84 (17%) participants in the nusinersen group and in 12/42 (29%) participants in the sham procedure group.

Oral olesoxime versus placebo

Bertini 2017 compared oral olesoxime versus placebo and reported outcomes at 24 months. See Table 6 for numerical results and Summary of findings 5.

Primary outcome

Change in disability score

Change in disability, measured using the MFM was a primary outcome in Bertini 2017. There was no evidence of a difference

in change in disability scores between the treatment and placebo groups (n = 160; very low-certainty evidence, downgraded one level for study limitations (risk of bias), one level for imprecision and one level for indirectness). The trial also measured motor function using the HFMS, with little or no difference in the change from baseline between the treatment and placebo groups (n = 160; low-certainty evidence, downgraded one level for study limitations (risk of bias) and one level for imprecision).

Secondary outcomes

Change in muscle strength

The study did not measure muscle strength.

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

Bertini 2017 measured quality of life using the PedsQL Neuromuscular Module. There was no evidence of a difference in quality of life between the olesoxime-treated group and the placebo group (n = 108; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Change in pulmonary function

Bertini 2017 measured the change in FVC in participants more than five years old. There was no evidence of a difference in pulmonary function between the treatment and placebo groups (n = 102; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

Two participants died, one in the olesoxime group and one in the placebo group. Deaths were reported not to be related to the study treatment. There were no other deaths and none of the participants reached the state of more than 16 hours' ventilation a day (n = 160; moderate-certainty evidence, downgraded one level for imprecision).

Adverse events, separated into severe and others

Bertini 2017 reported that 103 (95%) participants receiving olesoxime and 57 (100%) participants receiving placebo had at least one adverse event, with a total of 1104 adverse events in the olesoxime and 612 in the placebo group (n = 165; moderate-certainty evidence, downgraded one level for imprecision). Severe adverse events occurred in 18 (17%) participants in the olesoxime group and 14 (25%) participants in the placebo group (Bertini 2017).

Oral phenylbutyrate versus placebo

Mercuri 2007 compared oral phenylbutyrate versus placebo. See Table 7 for numerical results and Summary of findings 6.

Primary outcome

Change in disability score

Change in disability, measured on the HFMSE was a primary outcome in Mercuri 2007. There was no evidence of a difference for change in disability scores between the treatment and placebo groups (n = 90; low-certainty evidence, downgraded one level because of risk of bias and one level for imprecision).

Secondary outcomes

Change in muscle strength

Muscle strength was measured via quantitative myometry. There was no evidence of a difference for change in arm or leg megascore between the treatment and placebo groups (both measurements n = 70; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

The study did not measure quality of life.

Change in pulmonary function

Mercuri 2007 measured the change in FVC in participants aged more than five years. There was no evidence of a difference in pulmonary function between the treatment and placebo groups (n = 67; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

No deaths were reported (n = 107; low-certainty evidence, downgraded one level for imprecision and one level for risk of bias).

Adverse events, separated into severe and others

In Mercuri 2007, 2/54 participants treated with phenylbutyrate, compared with 1/53 participants treated with placebo had adverse events. Only one person in each group had a severe adverse event (n = 107; moderate-certainty evidence, downgraded one level for imprecision).

Subcutaneous somatotropin versus placebo

Kirschner 2014, which was a cross-over study, compared subcutaneous somatotropin with placebo. See Table 8 for numerical results and Summary of findings 7.

Primary outcome

Change in disability score

Kirschner 2014 measured disability as a secondary outcome using the HFMSE. Trial authors supplied additional data on the HFMSE for re-analysis.

There was no evidence of a difference between the treatment and placebo periods in the change in disability scores (n = 19; very low-

certainty evidence, downgraded two levels for risk of bias and one level for imprecision).

Secondary outcomes

Change in muscle strength

Muscle strength was measured via quantitative myometry (MMT). Trial authors supplied additional data upon request. There was no evidence of a difference between the treatment and placebo periods for change in muscle strength in the upper limbs (n = 19; low-certainty evidence) or in the lower limbs (n = 19; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

The trial report states that significant differences were not detected between somatotropin and placebo in quality of life measures, but the report does not specify the measures used or provide numerical data.

Change in pulmonary function

Kirschner 2014 measured the change in FVC in participants aged more than five years. Trial authors supplied additional data on pulmonary function for re-analysis. There was no evidence of a difference in pulmonary function between the treatment and placebo periods (n = 19; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached more than 16 hours' ventilation a day (n = 19; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Adverse events, separated into severe and others

In Kirschner 2014, 11 participants (55%) experienced 14 adverse events attributed to treatment while receiving somatotropin. Five events were classified as 'moderate' and two as 'severe', which resulted in termination of trial participation. In the placebo phase, a slightly smaller proportion of participants experienced adverse events, with seven participants reporting nine adverse events (n = 19; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Intravenous thyrotropin-releasing hormone versus placebo

Tzeng 2000 compared intravenous TRH versus placebo. See Table 9 for numerical results and Summary of findings 8.

Primary outcome

Change in disability score

The study did not measure change in disability score.

Secondary outcomes

Change in muscle strength

Tzeng 2000 measured muscle strength via quantitative myometry. There was no evidence of a difference for change in hand, arm, feet, leg or total muscle strength except in one participant treated with TRH (n = 9; very low-certainty evidence, downgraded one level for imprecision and two levels for study limitations).

No comparison was made by the study investigators between the treatment and placebo groups because the study size was considered too small.

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

The study did not measure quality of life.

Change in pulmonary function

The study did not measure pulmonary function.

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 9; low-certainty evidence, downgraded one level for imprecision and one level for study limitations).

Adverse events, separated into severe and others

In Tzeng 2000, the six participants treated with TRH had 12 adverse events, compared to no adverse events in the three participants in the placebo group (n = 9; very low-certainty evidence, downgraded two levels for imprecision and one level for study limitations and indirectness).

Oral valproic acid (valproate) plus acetyl-L-carnitine versus placebo

Swoboda 2010 compared oral valproate plus ACL versus placebo. See Table 10 for numerical results and Summary of findings 9.

Primary outcome

Change in disability score

Change in disability was a primary outcome in Swoboda 2010. The scale used was the GMFM. There was no evidence of a difference for change in disability scores between the treatment and placebo groups (n = 61; moderate-certainty evidence, downgraded one level for imprecision).

Secondary outcomes

Change in muscle strength

Swoboda 2010 measured change in muscle strength via quantitative myometry. There was no evidence of a difference for change in hand, arm, feet, leg or total muscle strength between the treatment and placebo groups (n = 16; low-certainty evidence,

downgraded two levels for imprecision because of very small sample size).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

Quality of life was measured in Swoboda 2010 with the Profile Pediatric Quality of Life Inventory. There was no evidence of a difference in quality of life between the treatment and placebo groups (n = 16; very low-certainty evidence, downgraded one level for risk of bias, one level for indirectness and one level for imprecision).

In Swoboda 2010 there was no statistically significant association between quality of life and change in MHFMS, but there was a non-significant trend towards deterioration of quality of life as MHFMS declined.

Change in pulmonary function

Swoboda 2010 measured the change in FVC in participants aged more than five years. There was no evidence of a difference in pulmonary function between the treatment and placebo groups. The trial was noted to have insufficient power to observe a statistically significant association (n = 24; low-certainty evidence, downgraded one level for risk of bias and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 61; moderate-certainty evidence, downgraded one level for imprecision).

Adverse events, separated into severe and others

In Swoboda 2010, 23/30 (77%) participants receiving treatment with valproic acid plus ALC had one or more adverse event compared to 18/31 (58%) participants in the placebo group. Severe adverse events occurred in 20% of the participants treated with valproic acid plus ALC and in 6% of the placebo group (n = 61; moderate-certainty evidence, downgraded one level for imprecision).

Oral valproic acid (valproate) versus placebo

Kissel 2014 compared oral valproic acid (valproate) versus placebo. See Table 11 for numerical results and Summary of findings 10.

Primary outcome

Change in disability score

Change in disability was a secondary outcome in Kissel 2014. The scale used was the SMAFRS. The trial authors made additional data available. There was no evidence of a difference for change in disability scores between treatment and placebo periods (n = 31; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Secondary outcomes

Change in muscle strength

Muscle strength was measured via quantitative myometry. There was no evidence of a difference for change in hand, arm, feet, leg or total muscle strength between treatment and placebo periods(n = 30; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Acquiring the ability to stand within one year after the onset of treatment

The study did not measure ability to stand.

Acquiring the ability to walk or improvement of walking within one year after the onset of treatment

The study did not measure ability to walk.

Change in quality of life

Change in quality of life was assessed with the mini-SIP. Additional data were made available by the trial authors for re-analysis. There was no evidence of a difference between treatment and placebo periods (n = 28; moderate-certainty evidence, downgraded one level for study limitations).

Change in pulmonary function

Kissel 2014 included only adults and measured the change in FVC. Additional data were made available by the trial authors for re-analysis. There was no evidence of a difference in pulmonary function between treatment and placebo periods (n = 24; low-certainty evidence, downgraded one level for study limitations and one level for imprecision).

Time from beginning of treatment until death or full-time ventilation

No deaths were reported and none of the participants reached the state of more than 16 hours' ventilation a day (n = 33; low-certainty evidence, downgraded one level for imprecision and one level for study limitations)

Adverse events, separated into severe and others

The trial reported 96 adverse events. Trial authors supplied additional information on the types and number of adverse events. Thirty of the adverse events occurred in the valproic acid treatment period and 60 occurred in the placebo treatment period. Two of the events led to early termination of trial participation. Additionally, there were five serious adverse events; two in the valproic acid treatment period and three in the placebo treatment period, but all five were classified as unrelated to treatment (Kissel 2014) (n = 33; low-certainty evidence, downgraded one level for imprecision and one level for study limitations).

DISCUSSION

Summary of main results

We found 10 randomised controlled trials (including 717 participants) with data available to evaluate the efficacy of drug treatment in people with SMA types II and III (Bertini 2017; Chen 2010; Mercuri 2007; Mercuri 2018 (CHERISH); Miller 2001; Kirschner 2014; Kissel 2014; Swoboda 2010; Tzeng 2000; Wong 2007). Two of these trials included only people with SMA type II (Mercuri 2007; Mercuri 2018 (CHERISH)), and one trial

only included ambulatory participants with SMA type III (Kissel 2014). Two RCTs included solely non-ambulatory participants with SMA types II and III (Swoboda 2010), and types II and IIIa (Bertini 2017). The treatments investigated were oral creatine, oral gabapentin, oral hydroxyurea, intrathecally injected nusinersen, oral olesoxime, oral phenylbutyrate, subcutaneous injections of somatropin, intravenous TRH, and oral therapy with valproic acid with or without oral acetyl-L-carnitine.

Intrathecally injected nusinersen was an effective treatment for the improvement of motor function in SMA type II (Mercuri 2018 (CHERISH)), with moderate-certainty evidence of improvement on the primary outcome (HFMSE) in the treatment group compared to a mean decline of motor scores in the sham-procedure group.

Although open and uncontrolled trials with other drugs had seemed promising, none of the other included nine trials showed any efficacy on any of the primary outcome measures (Bertini 2017; Chen 2010; Mercuri 2007; Miller 2001; Kirschner 2014; Kissel 2014; Swoboda 2010; Tzeng 2000; Wong 2007).

One RCT did not demonstrate efficacy of oral gabapentin in adults aged 21 years and older with SMA types II and III (Miller 2001). Efficacy of oral hydroxyurea was not established in one trial in 57 participants (Chen 2010).

One RCT of olesoxime in 165 participants with SMA types II and III suggested beneficial effects from olesoxime compared to placebo with stabilisation or slight improvement of motor function in post hoc responder analysis (dichotomous analysis), but there was no effect on the original primary or secondary outcomes (Bertini 2017). The RCT in 107 participants with SMA type II showed no efficacy after three months of treatment with phenylbutyrate (Mercuri 2007). The cross-over RCT of subcutaneous somatotropin in 20 participants with SMA types II and III showed no effect on muscle strength, motor function or pulmonary function (Kirschner 2014). Two trials investigated the effects of valproic acid in SMA, but both the trial of the combined therapy of valproic acid plus ALC in non-ambulatory and the trial of monotherapy with valproic acid showed no significant improvement of motor function and muscle strength compared to placebo treatment (Kissel 2014; Swoboda 2010).

Our confidence in these findings of little or no effect was very low for TRH; low to very low for olesoxime and somatotropin; low for valproic acid, phenylbutyrate, gabapentin and hydroxyurea; and moderate for nusinersen, creatine and valproic acid plus ALC.

Nine additional RCTs investigating 4-aminopyridine, ALC, CK-2121707 hydroxyurea, pyridostigmine, riluzole, RO6885247/RG7800, salbutamol and valproic acid were completed but no data for analysis were available at the time of writing and they could not be included in the final assessment (ASIRI 2008; CHICTR-TRC-10001093; Merlini 2007; MOONFISH 2014; Morandi 2013; NCT00568802; NCT01645787; NCT02644668; SPACE). We consider it unlikely that the results of Merlini 2007 (last update received 2007), NCT00568802 (last update received 2008) and ASIRI 2008 (last update received 2011) will be published in the future, because publication of the results has already been delayed many years.

Evidence from other studies in spinal muscular atrophy

We discuss the results of treatment with each of these drugs from unreported and non-randomised trials in SMA types II and III. Result of treatment in SMA type I is the topic of another Cochrane Review (Wadman 2019).

Carnitine

One RCT of treatment with ALC in 110 people with SMA types II and III is completed, but results are not available (Merlini 2007).

Celecoxib

One open-label trial in children and adults with SMA types II and III is planned to investigate the effect of different dosages of celecoxib on SMN protein levels in peripheral leukocytes (NCT02876094).

CK-2127107

One phase II RCT in 72 participants with SMA types II, III and IV to investigate safety and efficacy of CK-2127107 150 mg or 450 mg daily compared to placebo is completed, but results are not yet available (see Characteristics of studies awaiting classification; NCT02644668).

Creatine

There are no known trials or studies on creatine in SMA, apart from the trial included in this review (Wong 2007).

Gabapentin

In one large randomised, unblinded and uncontrolled trial with gabapentin in 120 participants with SMA types II and III, there was a trend for improvement in the strength in favour of gabapentin treatment observed after 12 months, with no effect on FVC or other functional tests (Merlini 2003).

Hydroxyurea

In one uncontrolled pilot trial in two people with SMA type I, five people with SMA type II and two people with SMA type III, hydroxyurea showed an improvement in muscle strength without adverse effects (Chang 2002). One larger randomised uncontrolled trial from the same investigators, included 33 people with SMA types II and III and treated them with three different doses of hydroxyurea for eight weeks (Liang 2008). This trial showed increased SMN gene expression and a trend towards improvement in clinical outcome measures.

Lamotrigine

One case series of two people with SMA types II (aged 28 years) and III (aged 37 years) described the use of lamotrigine 50 mg/day for 10 years and reported no deterioration in motor function over five years of treatment (Nascimento 2010).

Neuromuscular junction interactors

Two out of four participants with SMA type II and III reported improved endurance in daily activities after taking pyridostigmine 4 mg/day divided over multiple daily doses (Wadman 2012a). One placebo-controlled, cross-over trial in people with SMA types II to IV on the effect of the acetylcholine esterase inhibitor pyridostigmine versus placebo is completed, but results are not yet available (SPACE). One double-blind RCT in 12 participants with SMA type III aged 18 to 50 years has investigated the effect of 4-aminopyridine 10 mg twice daily versus placebo. This trial is completed and results are pending (NCT01645787).

Nusinersen

Two phase I/II studies (one open-label phase I study and its long-term extension) in 28 participants with SMA types II or III aged two to 14 years showed no safety or tolerability concerns with intrathecal nusinersen treatment (Chiriboga 2016; Darras 2013; Haché 2016). One RCT investigating one dose of nusinersen compared to a sham-procedure is ongoing and includes participants with atypical SMA type I, while excluding infants with a typical type I presentation (age at onset less than six months and having two *SMN2* copies) (EMBRACE 2015). One trial is including genetically confirmed, presymptomatic infants with probable SMA type I (NURTURE 2015). One trial in 34 children with SMA types II and III, aged two to 14 years that investigated the effects of three doses of nusinersen at four different doses has been completed, and results are pending (NCT01703988). One open-label trial in 52 children with SMA types II and III testing one dose of nusinersen is completed, but results are pending (NCT02052791). One open-label extension study (SHINE 2015) evaluated the effects of continuous treatment in patients previously participating in Mercuri 2018 (CHERISH) and Finkel 2017 (ENDEAR). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the use of nusinersen for SMA types I to IV.

Olesoxime

One open-label extension study with olesoxime was started (see OLEOS) to analyse long-term effects in non-ambulatory participants with SMA types II and III who participated in the previous study (Bertini 2017), but the pharmaceutical company announced that the trial and further development of olesoxime would be cancelled due to unsatisfactory results (Roche 2018).

Phenylbutyrate

One pilot study with phenylbutyrate 500 mg/kg/day using an intermittent schedule (seven days on and seven days off) in participants with SMA type II suggested positive effects on motor function after nine weeks of treatment with oral phenylbutyrate (Mercuri 2004). One multicentre phase I/II open-label trial intentionally evaluating multiple dosage levels of sodium phenylbutyrate to determine the maximum tolerated dose or the highest dose that can be safely given to children with SMA types II or III was terminated after the inclusion of nine participants due to poor compliance to the study drug administration of 500 mg/kg/day (NPTUNE01 2007). Analysis of data is pending but is probably underpowered. One phase I/II open-label study on sodium phenylbutyrate 450 mg/kg/day to 600 mg/kg/day in 14 presymptomatic infants genetically confirmed to have SMA with suspected SMA type I or II according to family history and *SMN2* copy number, has been completed, but results are pending (see STOPSMA 2007).

Riluzole

One study on pharmacokinetics of oral riluzole in 14 participants aged six to 20 years with SMA types II and III indicated that a dose of 50 mg/day of riluzole showed the same daily exposure of riluzole as in the indicated levels in previous trials with people with amyotrophic lateral sclerosis (Abbara 2011). One RCT with riluzole in 141 participants with SMA types II and III is completed, but has not been published and data were not available (ASIRI 2008).

Salbutamol

One case series of nine people with SMA type II treated with salbutamol showed positive effects on pulmonary function and patient perception of motor function (Pasanisi 2014; Tan 2011). In one pilot trial with 13 participants with SMA types II and III, there was a significant increase in muscle strength and pulmonary function after six months of salbutamol treatment (Kinali 2002). The next open-label trial involving 23 participants with SMA type II presented a significant improvement in functional scores after six and 12 months of treatment with salbutamol without any major adverse effects (Pane 2008). One open-label trial with 28 participants with SMA types I to III, aged one to 20 years, showed an increase in motor function (HFMS) and pulmonary function in 25% of participants and stability of functional scores in the rest of participants. The results of this study have not been published and are only available through conference reports (Prufer de Queiroz Campos Araujo 2010). One pilot study in 10 participants with SMA types II to IV reported an improvement on perceived motor function, disability and fatigue after salbutamol treatment (Giovannetti 2016). Pulmonary function, including maximal static inspiratory pressure, sniff nasal inspiratory pressure and slow vital capacity, showed effects of one-year treatment with daily oral salbutamol in seven children with SMA type II and III compared to a natural history cohort of children with SMA type II (Khirani 2017). Only one RCT with salbutamol is completed and suggested that salbutamol induced improvement of motor performance in the majority of the 45 adults with SMA type III. However, this trial has not been published and limited information is only available through conference abstracts (Morandi 2013).

Small molecules

RO6885247/RG7800

One phase I randomised, double-blind, placebo-controlled, multiple-dose study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RO6885247/RG7800 in people with SMA types I, II and III was started in November 2014, but later terminated due to potential safety reasons in December 2016 (for details see Studies awaiting classification; MOONFISH 2014).

RO7034067 or RG7916 (risdiplam)

One open-label trial including children and adults aged 12 to 60 years with SMA types II and III, previously treated with an *SMN2* anti-sense oligonucleotide, is recruiting participants (JEWELFISH 2017). One RCT with RO7034067/RG7916 has started recruiting children and adults with SMA types II and III (SUNFISH 2016). One trial will include genetically confirmed, presymptomatic infants with SMA (RAINBOWFISH), but has not started at time of writing this review.

Somatropin

There are no known trials or studies on somatotropin in SMA, apart from the trial included in this review (Kirschner 2014).

Thyrotropin-releasing hormone

A positive effect of TRH in SMA was considered since one uncontrolled study found improvement in motor function and electromyographic findings in participants with SMA types II and III after TRH therapy (Takeuchi 1994).

Valproic acid

Two case series and four open-label studies showed an increase of SMN transcripts levels in almost all participants with oral valproic acid, but only possibly a beneficial effect on pulmonary function and variable results on motor abilities and muscle strength (Darbar 2011; Kissel 2011; Saito 2014; Swoboda 2009; Tsai 2007; Weihl 2006). One retrospective uncontrolled case series reported improvement of motor function in seven adults with SMA types III and IV during treatment with valproic acid (Weihl 2006). In another retrospective case series, global muscle strength improved in two children and one adolescent with SMA types II and III, but there was no effect in three other participants (Tsai 2007). One prospective case series of seven people with SMA types II and III showed increased SMN transcripts, overall improvement of pulmonary function and improved motor function (Saito 2014). One open-label trial with 12-month treatment of valproic acid and L-carnitine in 33 children with SMA type III found no effects on motor function (Kissel 2011). One open-label trial with valproic acid in 42 children and adults with SMA types I, II and III showed only slight improvement in gross motor function in younger non-ambulatory type II children, variable responses of SMN transcripts in blood and carnitine depletion during treatment (Swoboda 2009). Results from the open-label study in 13 participants aged one to seven years with SMA types I to III are pending (SMART01).

There are four ongoing studies with valproic acid in SMA, including one RCT investigating monotherapy with valproic acid in children with SMA types I and II aged one to seven years (SMART02), one RCT investigating combined therapy of valproic acid plus L-carnitine in children aged two to 15 years with SMA types II and III (NCT01671384), and two open-label trials including people with SMA types I, II and III (JPRN-JapicCTI-163450 2016; SMART03).

Overall completeness and applicability of evidence

All trials included in this review investigated the effects of drug treatment in children or adults (or both) with SMA types II and III, in terms of disability, muscle strength, ability to stand or walk, quality of life, time to death or full-time ventilation and adverse events. The trials investigated 10 different treatments, additionally the inclusion criteria and outcome measures varied between trials, which makes it impossible to perform meta-analyses.

A major issue in SMA, irrespective of the investigated therapy, is the timing of the treatment in relation to its potential effect. Previous experimental studies suggested that there is a limited window of opportunity to rescue or stabilise motor neuron function in the early or presymptomatic stages of the disease. None of the 10 trials identified for inclusion in this review primarily included people who had just been diagnosed. One phase I/II study with phenylbutyrate in presymptomatic infants genetically confirmed to have SMA, and suspected to have SMA type I or II according to family history and *SMN2* copy number, has been completed and results are pending (STOPSMA 2007). One trial was started with nusinersen treatment in presymptomatic infants with genetically confirmed SMA (NURTURE 2015).

The practice of supportive care, e.g. pulmonary, nutritional and orthopaedic supportive therapy, in children and adults with SMA types II and III probably differs between centres and countries (Bladen 2014). Practice guidelines for the clinical care of children and adults with SMA are given in the consensus statement for standard care in SMA (Finkel 2018; Mercuri 2018). For future trials it is important that the level of supportive care is explicitly mentioned to avoid baseline differences in the treatment arms and between participating centres.

Certainty of the evidence

None of the included trials were completely free of bias according to the Cochrane 'Risk of bias' tool (Higgins 2011).

The randomisation method was not clear in four trials (Chen 2010; Kissel 2014; Tzeng 2000; Wong 2007). Allocation concealment was not clear in four trials (Chen 2010; Kissel 2014; Miller 2001; Wong 2007) and at high risk of bias in Tzeng 2000. Blinding of parents, participants and observers were adequate in all trials except Kissel 2014, for which the risk of bias related to blinding of participants and personnel and outcome assessors was unclear. We graded the risk of attrition bias high in four trials (Kirschner 2014; Mercuri 2007; Miller 2001; Swoboda 2010), and unclear in three trials (Bertini 2017; Kissel 2014; Wong 2007). Reporting bias was suspected in four trials (Bertini 2017; Chen 2010; Kirschner 2014; Tzeng 2000), and unclear in one trial (Miller 2001).

The cross-over design with potential carry-over effects in three studies placed two studies at unclear risk of bias (Kirschner 2014; Swoboda 2010), and one study at high risk of bias (Kissel 2014). Baseline differences resulted in potential bias in four trials, which we graded at either an unclear risk of bias (Mercuri 2018 (CHERISH); Swoboda 2010), or a high risk of bias (Bertini 2017; Wong 2007).

Grading unexplained heterogeneity or inconsistency of results was not possible, since we could not pool data in a meta-analysis for any drug treatment. We downgraded the evidence one level for imprecision when studies were small or included an insufficient number of participants according to the power analysis of the study.

One issue that is noteworthy and unique for SMA is that the phenotype of patients varies significantly among and within SMA types II and III. Additionally, *SMN2* copy number correlates with disease severity. Therefore, studies should consider SMA type and *SMN2* copy number as a stratification criterion. None of the included studies incorporated *SMN2* copy number in the inclusion criteria or subgroup analyses, which might have influenced results.

Motor assessments were all done with methods validated in SMA or other neuromuscular disorders. However, the disability scores and techniques to measure muscle strength currently used are possibly not sensitive enough to detect subtle changes in muscle strength and motor function, and may therefore underestimate or fail to detect a potential beneficial effect of treatment (type II error).

We are confident that we have minimised the risk of publication bias by evaluating all trial registries and screening trials and studies awaiting publication.

Potential biases in the review process

There may be some potential for bias in this review process as there were changes to the protocol. These included additions and deletions to the outcomes and alterations to the reporting of adverse events, as reported in Differences between protocol and review. None of these changes were made as a result of the findings

of the included studies but rather to improve the structure of the review.

All the included trials were relatively small and had a short-term follow-up period. We did not extensively report on adverse events. We could not exclude the possibility of missing uncommon adverse events in our review.

We are confident that we have identified all clinically relevant trials, as we conducted a comprehensive search of all published literature and clinical trial registries, and three of the review authors regularly attend international conferences on SMA.

The results of our review might be biased since, at the time of writing, the results had not been published from nine completed trials, investigating 4-AP (NCT01645787), ALC (Merlini 2007), CK-2127107 (NCT02644668), hydroxyurea (NCT00568802), pyridostigmine (SPACE), riluzole (ASIRI 2008), rat nerve growth factor (CHICTR-TRC-10001093), RO06885247/RG7800 (MOONFISH 2014), and salbutamol (Morandi 2013).

The review authors are investigators in trials of different drug treatments in SMA. The search and selection of trials were not, however, biased by the review authors' involvement in these trials. Data analysis of the creatine trial (Wong 2007, with Dr Iannaccone as investigator and author) was performed by Drs Wadman and Vrancken. Data analysis for the olesoxime trial was checked by Dr Iannaccone, as Drs Wadman, van der Pol and Vrancken were site investigators (Bertini 2017).

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there are no other systematic reviews considering the whole spectrum of drug treatments in SMA. Several reviews have also identified and discussed various drug treatments in SMA (Anderton 2015; Arnold 2013; Darras 2007; Lewelt 2012; Nurputra 2013; Stavarachi 2010; Swoboda 2007; Tisdale 2015), with some focusing specifically on preclinical studies (Seo 2013), genetic therapies (Donnelly 2012; Zanetta 2014), solely histone deacetylase inhibitor therapies (Mohseni 2013), SMN-inducing therapies (Kaczmarek 2015), or small molecule and molecular therapies (Zanetta 2014). Our conclusions are in line with these reviews.

Although we have tried to give an overview of the efficacy of drug treatment with gabapentin, creatine, nusinersen, valproic acid with and without acetylcarnitine, somatotropin, TRH, phenylbutyrate, olesoxime and hydroxyurea in preclinical studies, studies with animal models of SMA or studies in participants with SMA (Discussion), the overview on non-randomised and preclinical trials and studies was not based on a systematic review and potential studies might have been missed.

AUTHORS' CONCLUSIONS

Implications for practice

Nusinersen probably improves motor function in spinal muscular atrophy (SMA) type II (moderate-certainty evidence).

Creatine, gabapentin, hydroxyurea, phenylbutyrate, thyrotrophin releasing hormone, valproic acid and the combination of valproic acid and acetyl-L-carnitine probably have no clinically important effect on motor function in SMA II/III (low- to moderate-certainty evidence). Olesoxime and somatotropin may have no effect on motor function (low- to very low-certainty evidence). We are uncertain about the effect of thyrotropin-releasing hormone as the evidence is very low certainty.

Implications for research

Nusinersen is the only drug therapy for SMA for which there is moderate-certainty evidence of benefit. New therapies or treatment strategies should preferably either be compared to nusinersen or be evaluated as an add-on therapy to nusinersen.

Most trials investigating new therapies are focused on the early phases of the disease, since motor improvement or lack of decline is the easiest way to establish drug efficacy. However, therapies for those who already have a prolonged disease duration should also be sought to prevent disease progression, conserve motor function and improve quality of life.

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We used a standard template provided by Cochrane Neuromuscular to complete some of the mandatory sections of the methods.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bertini 2017

Methods	Randomised, placebo-controlled, double-blind trial
Participants	165 non-ambulatory participants with SMA types II or IIIa aged 3–25 years Inclusion criteria: • genetic diagnosis of SMA with homozygous deletion of SMN1 exon 7, or a heterozygous deletion accompanied by a point mutation on the other allele • MFM relative score (percentage of the maximum sum of both dimensions) of ≥ 15% (functional domain 1 (D1) plus functional domain 2 (D2) score) • HFMS score at baseline 3–38 (non-ambulatory); onset of symptoms at ≤ 3 years of age • ability to take the study treatment (tested at screening after informed consent) Exclusion criteria: • evidence of renal dysfunction, blood dysplasia, hepatic insufficiency, symptomatic pancreatitis • congenital heart defect • history of metabolic acidosis • hypertension • significant central nervous system impairment, or neurodegenerative or neuromuscular disease other than SMA • any clinically significant ECG abnormality • use of medications intended for the treatment of SMA • inability to meet study visit requirements or co-operate reliably with functional testing • surgical spinal rod or fixation for scoliosis within the past 6 months or anticipated need of rod or fixation within 6 months of enrolment
Interventions	Oral liquid olesoxime (TRO19622: cholest-4-en-3-one, oxime) 10 mg/kg once a day or placebo Treatment duration: 24 months
Outcomes	Primary outcome: change over 24 months in functional outcome score D1+D2 of MFM Secondary outcomes: change in total MFM score, HFMS, electrophysiological measures (CMAP and MUNE), pulmonary function (FVC), quality of life (PedsQL), and Global Clinical Impression from baseline, responder analysis of MFM, laboratory assessments, ECG and adverse events
Funding	AFM-Téléthon and Trophos SA (a wholly owned member of the Hoffmann La Roche Group since 2015)

Bertini 2017 *(Continued)*

Conflicts of interest	Several investigators declared grants and consultancy fees from Hoffmann La Roche, Trophos and other commercial entities. 8 investigators were current or former employees of Trophos or Hoffmann La Roche, 3 were stockholders and 2 authors were named on a patent pending for olesoxime. Roche also funded medical writing support.
Notes	ClinicalTrials.gov id: NCT01302600

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned, centrally generated with validated randomisation software (SAS version 9.2).
Allocation concealment (selection bias)	Low risk	Computer-generated allocation by independent statistician.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and all investigators, site personal and sponsor study personal was ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and all investigators, site personal and sponsor study personal was ensured.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 participants withdrew for unknown reasons.
Selective reporting (reporting bias)	High risk	Data were dichotomised post hoc. Investigators were employees of the pharmaceutical company and they were involved in data collection and analysis.
Other bias	High risk	Primary outcome measure was used in 2 different forms (MFM-32 and MFM-20) and, therefore, not truly comparable. Treatment groups have differences in included age ranges.

Chen 2010

Methods	Randomised, placebo-controlled, double-blind trial
Participants	57 participants aged ≥ 5 years who fulfilled international classification criteria for SMA types II or III and with a homozygous deletion of the SMN1 gene Inclusion criteria: • having type 2 or 3 SMA, aged ≥ 5 years; and with a confirmed genetic diagnosis owing to a homozygously deleted *SMN1* gene Disease severity was categorised according to the International Classification for SMA, which is based on age at disease onset and maximum function. Exclusion criteria: • evidence of impaired renal, hepatic or haematopoietic function • history of severe antenatal asphyxia • congenital anomalies other than SMA

Chen 2010 *(Continued)*

	• intermittent (≥ 16 hours per day) or continuous requirement for mechanical ventilation • prior major surgery or any procedure needing generalised anaesthesia during the past 6 months • participation in any other clinical trial or administration of any agents that potentially benefit SMA within the past 6 months
Interventions	Oral hydroxyurea in escalating dose from 10 mg/kg to 20 mg/kg over 8 weeks (5 mg/kg increase per 4 weeks) or placebo in increasing dose over 8 weeks Duration of treatment: 18 months Follow-up: 6 months post-treatment
Outcomes	Change in functional score (GMFM), change in functional score in non-ambulatory patients (HFMS), change in muscle strength (MMT), change in pulmonary function (FVC), adverse events
Funding	Quote: "Supported by Department of Health, Executive Yuan, Taiwan (DOH96-TD-I-111-TM013) and in part by Sun's KMU-SMA fund."
Conflicts of interest	Most authors reported research support from Department of Health, Executive Yuan, Taiwan and Sun's KMU-SMA fund. 2 authors reported patents regarding hydroxyurea treatment for SMA and method for diagnosis of SMA.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned. No methods of randomisation described.
Allocation concealment (selection bias)	Unclear risk	No details of randomisation given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, families, investigators, study co-ordinators, evaluators and statisticians were blinded. Randomisation unit and study pharmacist were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, families, investigators, study co-ordinators, evaluators and statisticians were blinded. Randomisation unit and study pharmacist were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	Data on muscle strength dichotomised post hoc.
Other bias	Low risk	None identified.

Kirschner 2014

Methods	Randomised, double-blind, placebo-controlled cross-over trial

Kirschner 2014 *(Continued)*

Participants	20 participants with SMA types II and III, genetically confirmed with SMN1- deletion or mutation, aged 6–36 years Inclusion criteria: • 6–36 years of age, genetically confirmed diagnosis of SMA verifying SMN1 deletion or mutation • types II or III SMA (independent sitting is or was possible) • the physical ability to co-operate on assessment of at least the primary outcome measure Exclusion criteria: • diagnosis of growth hormone deficiency • treatment with any medication that could potentially affect muscle strength within 8 weeks prior to trial onset • pregnancy, lactation or if the woman was of child-bearing age and sexually active without verified contraception • participation in another clinical trial within 3 months of trial starting • any contraindication for growth hormone treatment
Interventions	Subcutaneous somatotropin (first week dose 0.015 mg/kg/day; week 2–12 dose 0.03 mg/kg/day) or placebo subcutaneous (first week dose 0.015 mg/kg/day; week 2–12 dose 0.03 mg/kg/day) Treatment of 12 weeks with 1 treatment (somatropin or placebo) followed by 8 weeks' washout, afterwards second cross-over treatment period (somatropin or placebo) of 12 weeks is started
Outcomes	Change in quantitative muscle strength of upper limb using hand-held myometry in elbow flexion and handgrip, change in quantitative muscle strength of lower limb, muscle strength with MMT in 7 muscles, change in motor function (HFMSE), change in Gowers' time, change in qualitative Gowers' manoeuvre, change in pulmonary function (FVC and peak cough flow), adverse events
Funding	Quote: "NovoNordisk Pharma GmbH provided the trial drug and some financial support for conducting this trial. NovoNordisk had no influence on the trial design, how the trial was conducted or the data analysis."
Conflicts of interest	Author conflicts of interest not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned. Computer-generated allocation by central pharmacy.
Allocation concealment (selection bias)	Low risk	Computer-generated allocation by central pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, physicians and physiotherapists were blinded. Statistical analysis of primary outcome was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, physicians and physiotherapists were blinded. Statistical analysis of primary outcome was blinded.
Incomplete outcome data (attrition bias)	High risk	3 participants withdrew during somatotropin treatment. They were included in the modified ITT (unknown method) analysis.

Kirschner 2014 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Quality of life is mentioned as an outcome, but no scale is mentioned. However, the report states that the trial found no difference between somatotropin and placebo groups in quality of life.
Other bias	Unclear risk	Potential bias from cross-over study design; cross-over design implies risk of carryover effect.

Kissel 2014

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	33 ambulatory adults with SMA type III Inclusion criteria: • ambulatory adults with SMA 3 aged 18–60 years • diagnosis of SMA must have been documented by the homozygous deletion of both SMN1 genes on standard genetic tests for the disorder. Patients must have been able to walk 30 feet without assistance (i.e. no sticks, walkers) • interest in participating and the ability to meet the study requirements • women of child-bearing age were required to be on contraception or abstain while participating in the study Exclusion criteria: • co-existing medical conditions that precluded travel, testing or study medications • participation in a treatment trial for SMA in the 3 months prior to this trial, or plan to enrol in any other treatment trial during this study • requirement for any mechanical respiratory support > 12 hours per day • inability to meet visit requirements or co-operate reliably with functional testing • mental or legal incapacitation from giving informed consent, or inability to read and understand written material including in the consent form • abnormalities in baseline blood testing beyond established values • use of medications or supplements which interfere with valproic acid metabolism, or are hypothesised to have a beneficial effect in SMA animal models or human neuromuscular disorders within 3 months of study enrolment, including riluzole, creatine, butyrate derivatives, growth hormone, anabolic steroids, albuterol, anticonvulsants or other histone deacetylase inhibitors
Interventions	Oral valproic acid 10–20 mg/kg/day (doses adequate to reach serum levels 50–100 mg/dL) divided over 2–3 doses or placebo orally Cross-over of treatment after 6 months for a consecutive period of 6 months
Outcomes	Change in maximum voluntary isometric contraction testing for separate muscles (bilateral elbow flexors, elbow extensors, knee flexors, knee extensors and grip) and total muscle score, change in muscle strength measured by hand-held dynamometer of elbow flexors/extensors and knee flexors/extensor, change in SMAFRS, change in CMAP of ulnar nerve, change in mRNA levels, change in SMN protein levels, change in pulmonary function (FVC, FEV_1, MIP), change in muscle mass measured by DEXA, change in endurance assessed through 6-minute walk test, change in function assessed in time to climb 4 standard stairs, change in mini-SIP, adverse events
Funding	Quote: "Funded by Families of Spinal Muscular Atrophy and also by grants from the Center for Clinical and Translational Sciences, University of Utah (UL1RR025764), and the Center for Clinical and Translational Sciences, Ohio State University (UL1RR025755)."

Kissel 2014 *(Continued)*

	Abbott Pharmaceuticals provided valproic acid and placebo
Conflicts of interest	Authors reported receipt of grants and funding from Families of SMA and other non-governmental, charitable, governmental, academic and pharmaceutical company sources. 2 authors report receipt of drugs from Abbott Pharmaceuticals for clinical trials in SMA.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned. Unknown method. Since the trial was part of the previous Carni-VAL-I trial and most procedures were the same, one could suppose there was central randomisation by telephone; however, this was not exactly stated in the article or supplementary material.
Allocation concealment (selection bias)	Unclear risk	Randomly assigned. Unknown method. Since the trial was part of the previous Carni-VAL-I trial and most procedures were the same, one could suppose there was central randomisation by telephone; however, this was not exactly stated in the article or supplementary material.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants, physicians and investigators were blinded. 1 investigator was not blinded. Study compliance (tablet counts and valproic acid levels) were checked by unblinded investigator.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants, physicians and investigators were blinded. 1 investigator was not blinded. Study compliance (tablet counts and valproic acid levels) were checked by unblinded investigator.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants withdrew, but were included in ITT analysis.
Selective reporting (reporting bias)	Low risk	Incomplete data reported in article, but data available on request.
Other bias	High risk	Potential bias by design: cross-over design implies risk of carryover effect. No report on a washout period between the 2 treatment periods.

Mercuri 2007

Methods	Randomised, placebo-controlled, double-blind trial
Participants	107 participants who fulfilled international classification criteria for SMA type II Inclusion criteria: • diagnosis confirmed by genetic analysis with homozygous deletion of *SMN1* • SMA 2 was classified according to the International Classification for SMA, based on age at disease onset and maximum function achieved, i.e. age at onset over 6 months and being able to sit unsupported but not to walk Exclusion criteria: • participation in other pharmacological trials (e.g. albuterol) in the year before our trial started

Mercuri 2007 *(Continued)*

	• undergone corrective surgery for scoliosis
Interventions	Phenylbutyrate 500 mg/kg/day 7 days orally, divided in 5 doses using an intermittent schedule (7 days on and 7 days off) or placebo Duration of treatment: 3 months Follow-up: 3 months
Outcomes	Functional score (HFMS), change in functional score. Subgroup aged > 5 years: change in muscle strength arm and leg (myometry), change in pulmonary function (FVC), adverse events
Funding	Financial support from Famiglie SMA, Italy and Associazione per lo Studio delle Atrofie Spinali Muscolari Infantili (ASAMSI) Fyrklövern Scandinavia AB, Sweden provided triButyrate Medication provided by pharmaceutical company, but no details about the involvement of the company in study procedures.
Conflicts of interest	Quote: "The authors report no conflicts of interest."
Notes	Muscle strength was measured bilaterally for elbow flexion, hand grip and 3-point pinch. Muscle strength was measured bilaterally for knee flexion and knee extension.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned. Central allocation.
Allocation concealment (selection bias)	Low risk	Central allocation. Only randomisation unit and pharmacy had access to assignment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only randomisation unit and pharmacy had access to assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only randomisation unit and pharmacy had access to assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Myometry and FVC were measured in children aged > 5 years, but a different number of children were reported in the 2 groups. No report on explaining this difference. Unclear reports on adverse events. Quote: "The efficacy analyses were conducted according to the original randomization assignment (intention to treat), using the last observation carried forward approach for missing follow-up data"
Selective reporting (reporting bias)	Low risk	There was clear evidence that reported results corresponded to all intended outcome measurements.
Other bias	Low risk	No other bias identified

Mercuri 2018 (CHERISH)

Methods	Randomised sham-procedure controlled, double-blind trial. Randomisation 2:1 (nusinersen:sham procedure)
Participants	126 participants with SMA types II, aged 2–12 years Inclusion criteria: • informed consent from parent or guardian and, if required, from participant • medically diagnosed with SMA • onset of clinical signs and symptoms consistent with SMA at > 6 months of age • able to sit independently, but has never had the ability to walk independently • HFMSE ≥ 10 and ≤ 54 at screening • able to complete all study procedures, measurements and visits and parent or guardian and participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator • estimated life expectancy > 2 years from screening, in the opinion of the Investigator • meets age-appropriate institutional criteria for use of anaesthesia and sedation, if use is planned for study procedures • satisfies study contraceptive requirements, if of reproductive age Exclusion criteria: • respiratory insufficiency, defined by the need for invasive or non-invasive ventilation for > 6 hours during a 24-hour period, at screening • requires a gastric feeding tube, via which the majority of feeds are given • severe contractures or severe scoliosis evident on x-ray • hospitalisation for surgery (i.e. scoliosis surgery, other surgery), pulmonary event or nutritional support within 2 months of screening or planned during the duration of the study • presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period • history of brain or spinal cord disease, including tumours, or abnormalities by magnetic resonance imaging or computerised tomography that would interfere with the lumbar puncture procedures or CSF circulation • presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter • history of bacterial meningitis • dosing with nusinersen in any previous clinical study • prior injury or surgical procedure which impacts the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline • clinically significant abnormalities in haematology or clinical chemistry parameters or ECG at screening • treatment with another investigational drug (e.g. oral albuterol or salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate, etc.), biological agent, or device within 1 month of screening or 5 half-lives of study agent, whichever is longer. Treatment with valproate or hydroxyurea within 3 months of screening. Any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation • ongoing medical condition that would interfere with the study. Examples are medical disability that would interfere with the assessment of safety or compromise the ability of the participant to undergo study procedures
Interventions	Intrathecal injection with nusinersen 12 mg or sham procedure
Outcomes	Change in HFMSE, achievement of new motor milestones, change in Upper Limb Module Test, vital signs, weight changes, laboratory changes, ECG
Funding	Ionis Pharmaceuticals and Biogen Inc

Mercuri 2018 (CHERISH) *(Continued)*

Conflicts of interest	Investigators collected data, which were held and analysed by Biogen. The first manuscript was written by the authors and the senior industry author of Biogen, medical-writing assistance was paid for by Biogen.
Notes	As of December 2016 the study was stopped and participants were transitioned to the open-label SHINE study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by central and electronic procedure.
Allocation concealment (selection bias)	Low risk	Computer-generated allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study personnel who deliver the treatment were not involved in the assessments of participants. Key personnel for assessments and parents of participants were not present during procedure.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study personnel who deliver the treatment were not involved in the assessments of participants. Key personnel for assessments and parents of participants were not present during procedure.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Trial stopped early for benefit on the basis of interim analyses. ITT and efficacy outcomes reported. Data imputed for ITT analyses. Supplementary data report sensitivity analyses. Quote: "Sensitivity analyses of the primary end point using final data were consistent with the results of the final analysis."
Selective reporting (reporting bias)	Low risk	Protocol available. There was clear evidence that reported results corresponded to all intended outcome measurements. Extensive data reporting in article and supplementary material.
Other bias	Unclear risk	Baseline differences with more severely affected children in the nusinersen-treated group.

Miller 2001

Methods	Randomised, placebo-controlled, double-blind trial (2 × 2 block design)
Participants	84 participants who fulfilled international classification criteria for SMA types II or III and have an homozygous deletion of the *SMN1* gene Inclusion criteria: • clinical diagnosis of SMA, type II or III • aged ≥ 21 years • homozygous defect in the *SMN* gene • FVC > 35% of predicted • the ability to sit unsupported at some time in the disease course • elbow flexion or handgrip strength (or both) > 3 kg

Miller 2001 *(Continued)*

	Exclusion criteria: • not mentioned
Interventions	Gabapentin 1200 mg 3 times a day or placebo Duration of treatment: 12 months Follow-up: at quarterly time intervals while on treatment
Outcomes	Change in disability score (SMAFRS), change in muscle strength, development of walking, change in pulmonary function (FVC), change in quality of life (SIP), adverse events
Funding	Andrew's Buddies, MDA, Warner-Lambert, and Families of SMA
Conflicts of interest	Not stated
Notes	Muscle strength of elbow flexion and hand grip was measured bilaterally.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned. Randomisation in blocks of 4 participants (2 placebo, 2 gabapentin) with equalised randomisation per centre. No methods of randomisation described.
Allocation concealment (selection bias)	Unclear risk	Randomisation performed by research pharmacist. Precise method of allocation concealment not known.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only research pharmacist was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only research pharmacist was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for dropout of 19 participants not mentioned. ITT analysis performed with a different number of participants than initially included.
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported.
Other bias	Low risk	None identified

Swoboda 2010

Methods	Randomised, placebo-controlled, double-blind trial
Participants	61 non-ambulatory participants with SMA types II or III Inclusion criteria: • confirmed genetic diagnosis of 5q SMA

Swoboda 2010 *(Continued)*

	• SMA 2 or non-ambulatory SMA 3: SMA 2 participants must have been able to sit independently for ≥ 3 seconds without support • aged 2–8 years at time of enrolment Exclusion criteria: • MHFMS for children with SMA (MHFMS-SMA) total score ≤ 2 or ≥ 37 • need for bilevel positive airway pressure support > 12 hours per day • spinal rod or fixation for scoliosis or anticipated need within 6 months of enrolment • inability to meet study visit requirements or co-operate reliably with functional testing • presence of predefined biochemical or haematological abnormalities in blood work • co-existing medical conditions that contraindicate travel, testing or study medications • use of medications or supplements which interfere with valproic acid or carnitine metabolism, increase the potential risks of these medications or were hypothesised to have a beneficial effect in SMA animal models or human neuromuscular disorders within 3 months of study enrolment (specifically, concomitant use of riluzole, creatine, butyrate derivatives, growth hormone, anabolic steroids, daily albuterol use, anticonvulsants or other histone deacetylase inhibitors would preclude enrolment) • current use of either valproic acid or carnitine through participation in another study or been prescribed by their attending physician (if study participant is taking valproic acid or carnitine then participant must have gone through a washout period of 12 weeks before been enrolled into the study) • body mass index ≥ 90th percentile for age
Interventions	Oral liquid carnitine 50 mg/kg/day in 2 doses in combination with oral valproic acid capsules in 2–3 doses to maintain overnight serum level trough 50–100 mg/dL or liquid placebo twice daily in combination with placebo capsule 2–3 times a day Duration of treatment: 12 months in active treatment and 6 months in placebo group. The placebo group switched to active treatment after 6 months per protocol Total follow-up: 12 months
Outcomes	Primary: safety, motor function assessments, change in functional score (MHFMS) Secondary: include change in quality of life (PedsQL), change in innervation via maximum ulnar CMAP, adverse events. Change in muscle strength and change in pulmonary function were measured in participants aged ≥ 5 years
Funding	Quote: "Abbott Pharmaceutical provided VPA [valproic acid] and placebo, and Sigma-Tau Pharmaceutical provided L-carnitine, at no cost."
Conflicts of interest	Quote: "The authors have declared that no competing interests exist."
Notes	Baseline differences in body mass index and gender between the different treatment groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned using a permuted block design balancing for institution.
Allocation concealment (selection bias)	Low risk	Randomisation was performed using a permuted block design balancing for institution. Randomisation was performed centrally by telephone.
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel. Medical monitor was unblinded.

Swoboda 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel. Medical monitor was unblinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all outcome measures are available for analysis. Missing data were not fully explained.
Selective reporting (reporting bias)	Low risk	Protocol available. There was clear evidence that reported results correspond to all intended outcome measurements.
Other bias	Unclear risk	Partial cross-over design after 6 months.

Tzeng 2000

Methods	Randomised (ratio 2:1), placebo-controlled, double-blind trial
Participants	9 participants who fulfilled international classification criteria for SMA types II or III Inclusion criteria: • aged 4–10 years, confirmation of chromosome 5q *SMN* gene deletion • parent or guardian willing and able to comply with study requirements and give consent • participant willing to comply with the study Exclusion criteria: • history of epilepsy • concurrent participation in another investigational drug trial or participation in 1 during the previous 30 days • abnormal serum chemistries in the initial screening • the inability to rapidly contact or be contacted by the investigator in case of emergency
Interventions	Thyrotropin-releasing hormone 0.1 mg/kg intravenous once a day or placebo Duration of treatment: 29 days of treatment over a 34-day period Follow-up: 35 days
Outcomes	Change in muscle strength (dynamometry), adverse events
Funding	Quote: "Supported, in part, by Ferring Laboratories, Inc., Suffern, New York, the manufacturer of Thyrel™ who made the study medication, Thyrel™, available without cost to the subjects, and, in part, by grant H133 P 70011, Advanced Multidisciplinary Fellowship in Rehabilitation Outcomes Research to the Department of Physical Medicine and Rehabilitation, UMDNJ-New Jersey Medical School, from the National Institute on Disability and Rehabilitation Research."
Conflicts of interest	Not reported
Notes	Groups were not equal at baseline, with only women, only SMA II and older participants in the placebo group. Muscle strength was measured bilaterally of deltoid, biceps, triceps, wrist extension, hand grip, hip flexion, knee extension and knee flexion.
Risk of bias	

Tzeng 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned (2:1). Patients randomised by double coin flip for each patient. Any heads-tails combination was a participant; a tails–tails combination was a control; and a heads–heads combination was rejected and the flip repeated. Potential bias by inclusion of first arrival method. Quote: "Once either the control or subject group was full, all subsequent arriving patients were placed into the remaining group."
Allocation concealment (selection bias)	High risk	Randomisation done on a first arrival basis. Quote: "Once either the control or subject group was full, all subsequent arriving patients were placed into the remaining group."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators and participants were blinded. Only the pharmacist was unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators and participants were blinded. Only the pharmacist was unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	High risk	All outcomes were reported. The statistical analysis plan is limited and unclear.
Other bias	Low risk	None identified.

Wong 2007

Methods	Randomised, placebo-controlled, double-blind trial
Participants	55 participants who fulfilled international classification criteria for SMA types II or III Inclusion criteria: • aged 2–18 years • clinical diagnosis of SMA with confirmed mutations of the *SMN1* gene • FVC ≥ 20% of predicted for age • < 15% variance on test–retest of QMT in ≥ 1 muscle group (for participants aged > 5 years) • postpubertal sexually active girls must have had a negative pregnancy test Exclusion criteria: • any evidence of renal dysfunction • central nervous system damage • neurodegenerative or neuromuscular disease other than SMA • a requirement for mechanical ventilation ≥ 16 hours a day • use of creatine or any experimental substance such as riluzole within 90 days of entering the study
Interventions	Creatine: aged 2–5 years, 2 g once a day or placebo; age 5–18 years, 5 g once a day or placebo

Wong 2007 *(Continued)*

	Duration of treatment: 6 months Follow-up: 9 months
Outcomes	2–5 years and 5–18 years: change in disability score (GMFM), change in quality of life, adverse events 5–18 years: change in quantitative muscle strength (QMT), change in pulmonary function
Funding	National Institutes of Health, the Muscular Dystrophy Association, and Andrew's Buddies Experimental and Applied Sciences; Golden, Colorado supplied creatine
Conflicts of interest	Not reported
Notes	Creatine group at baseline slightly weaker; follow-up inadequate (> 20% dropout rate and < 9 months' follow-up). Muscle strength was measured bilaterally for hand grip, elbow flexion, knee extension and knee flexion according to the Richmond Quantitative Measurement System

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, method of randomisation unknown.
Allocation concealment (selection bias)	Unclear risk	Randomisation at central site. Method not known.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, families, investigators, evaluators and study co-ordinators blinded; the study statistician blinded to group membership.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, families, investigators, evaluators and study co-ordinators blinded; the study statistician blinded to group membership.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High dropout rate partially described.
Selective reporting (reporting bias)	Low risk	Outcome measurements were limited and inconsistent in the published report, but the trialists provided additional data for analysis.
Other bias	Unclear risk	None identified.

CMAP: compound muscle action potential; CSF: cerebrospinal fluid; DEXA: dual energy X-ray; ECG: electrocardiogram; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GMFM: Gross Motor Function Measure; HFMS(E): Hammersmith Functional Motor Scale (Expanded); ITT: intention-to-treat; MFM: Motor Function Measure; MHFMS: Modified Hammersmith Functional Motor Scale; mini-SIP: mini-Sickness Impact Profile; MIP: maximum inspiratory pressure; MMT: manual muscle testing; mRNA: messenger ribonucleic acid; MUNE: motor unit number estimation; PedsQL: Pediatric Quality of Life Inventory; QMT: quantitative muscle testing; SMA: spinal muscular atrophy; SMAFRS: Spinal Muscular Atrophy Functional Rating Scale; SMN: survival motor neuron.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbara 2011	Riluzole. Non-randomised, open-label study to assess pharmacokinetics of riluzole in people with SMA types II and III.
Brahe 2005	Phenylbutyrate. Not randomised, not controlled. Pilot trial. Study on the effect of phenylbutyrate on human SMN expression in blood.
Brichta 2006	Valproic acid. Not randomised, not controlled. Pilot trial. Study on the effect of valproic acid on human SMN expression in blood.
Chang 2002	Hydroxyurea. Not randomised, not controlled. Pilot trial. Study on the effect of hydroxyurea on clinical manifestations and human SMN expression in blood.
Chiriboga 2016	Nusinersen. Phase 1, 4 groups, dose-escalating trial. Not randomised, not controlled.
Darbar 2011	Valproic acid. Open-label trial, not controlled. No placebo given.
EMOTAS 2014	Pyridostigmine. Open-label trial. Not randomised, not controlled. Study ongoing, but can be excluded.
Folkers 1995	Coenzyme Q10. Not randomised, not controlled. Observational study that included 1 participant with SMA type III/IV.
Giovannetti 2016	Salbutamol. No placebo given.
JEWELFISH 2017	RG7916 or RO7034067. Open-label trial, no placebo given. Study ongoing, but can be excluded.
JPRN-JapicCTI-163450 2016	Sodium valproate. Open-label trial, no placebo given. Study ongoing, but can be excluded.
Kato 2009	Thyrotropin. Case report.
Khirani 2017	Salbutamol. Not randomised, not controlled. Pilot trial.
Kinali 2002	Albuterol. Not randomised, not controlled. Pilot trial.
Kissel 2011	Valproic acid. Open-label trial, not controlled.
Liang 2008	Hydroxyurea. Not controlled.
Mercuri 2004	Phenylbutyrate. Not randomised, not controlled. Pilot trial.
Merlini 2003	Gabapentin. Not controlled (no placebo given, compared treatment with no treatment, not blinded).
Nascimento 2010	Lamotrigine. Case series. Not controlled, not randomised.
NCT01703988	Nusinersen. Open-label study. Study completed; results pending.
NCT02052791	Nusinersen. open-label. Study completed; results pending.

Study	Reason for exclusion
NCT02876094	Celecoxib. Open-label, non-randomised study. Primary outcome SMN protein level, no clinical scores or evaluation. Study ongoing, but can be excluded.
NCT03709784	Nusinersen. Observational study in adults treated with nusinersen. Study ongoing, but can be excluded.
NPTUNE01 2007	Sodium phenylbutyrate. Dose-escalating study. Non-randomised, not controlled. No placebo given. Trial terminated due to poor compliance with study drug administration.
OLEOS	Olesoxime. Not randomised, not controlled. No placebo given. Only people who participated in previous trials (TRO19622CLEQ11150-1 or TRO19622CLEQ1275-1) to be included. Study ongoing, but can be excluded.
Pane 2008	Salbutamol. Not randomised, not controlled. Pilot trial.
Piepers 2011	Valproic acid. Not controlled, not randomised. Case series.
Prufer de Queiroz Campos Araujo 2010	Salbutamol. Pilot trial. Not controlled (no placebo given), not randomised.
Saito 2014	Valproic acid. Case series. Not controlled (no placebo given), not randomised.
SHINE 2015	Nusinersen. Open-label, not randomised. No placebo or sham-procedure given. Study ongoing, but can be excluded.
SMART01	Valproic acid. Open-label trial. Not randomised, not controlled (no placebo given). Study completed, no published data yet.
SMART03	Valproic acid. Open-label trial. Not randomised, not controlled (no placebo given). Study recruiting participants, but can be excluded.
Swoboda 2009	Valproic acid and carnitine. Not controlled (no placebo given). Open-label trial.
Tan 2011	Salbutamol. Not randomised, not controlled. Case series.
Tsai 2007	Valproic acid. Not randomised, not controlled.
Weihl 2006	Valproic acid. Not randomised, not controlled. Retrospective study on people with SMA types III and IV.

SMA: spinal muscular atrophy; SMN: survival motor neuron.

Characteristics of studies awaiting assessment *[ordered by study ID]*

ASIRI 2008

Methods	Randomised, placebo-controlled, double-blind trial
Participants	People with SMA types II or III, aged 6–20 years.

ASIRI 2008 *(Continued)*

Interventions	Riluzole 50 mg/day orally or placebo Duration of treatment: 24 months Follow-up: 24 months
Outcomes	Motor function (MFM scale), spirometry (FVC), Measure of Functional Independence, adverse events and tolerance evaluation.
Notes	Study completed (December 2011), but no results available.

CHICTR-TRC-10001093

Methods	Randomised, parallel, controlled trial. Placebo was mentioned, but unknown if the trial was placebo-controlled.
Participants	40 participants with SMA type II, aged 3–8 years
Interventions	Rat nerve growth factor injection for 6 months
Outcomes	Change in Pediatric Evaluation of Disability Inventory, change in electromyogram.
Notes	Study completed, but no results available. Unknown date of completion; last update received April 2017 on WHO International Clinical Trials Registry Platform.

Merlini 2007

Methods	Randomised, placebo-controlled, double-blind trial
Participants	110 participants with SMA types II or III, aged ≥ 4 years
Interventions	Acetyl-L-carnitine 50 mg/kg/day (maximum 3 g/day) (route not mentioned) or placebo Duration of treatment: 9 months Follow-up: 12 months
Outcomes	Change in muscle strength arm and leg (myometry), change in functional score (time to walk 10 m and to arise from floor), change in pulmonary function (FVC), change in quality of life (Short Form-36 Health Survey questionnaire (SF-36) or Childhood Health Assessment Questionnaire.
Notes	Study status unknown (last report on trial notified in 2007). No results available

MOONFISH 2014

Methods	Phase I, randomised, double-blind, placebo-controlled trial
Participants	64 participants with SMA types I, II or III, aged 2–55 years or < 7 months
Interventions	RO6885247 orally once daily for 12 weeks or placebo orally once daily for 12 weeks

MOONFISH 2014 *(Continued)*

Outcomes	Safety (incidence of adverse events), pharmacokinetics (plasma concentrations of RO6885247 and RO6885247 exposure), pharmacodynamics (SMN protein levels in blood and in vivo splicing of SMN2 mRNA in blood), effect on CMAP, effect on electrical impedance myography.
Notes	Recruitment of participants suspended since April 2015 for safety reasons. In parallel to the MOONFISH trial, Hoffmann-La Roche have been investigating the effects of the long-term use of RG7800 in animals. These animal studies are a standard requirement in the development of new medicines. In this study, they observed an unexpected safety finding in the eye of animals and subsequently immediately suspended dosing in the MOONFISH trial as a precautionary measure. Trial terminated in July 2015. No results available at time of writing.

Morandi 2013

Methods	Randomised, placebo-controlled, double-blind trial
Participants	45 adults with SMA type III
Interventions	Salbutamol or identical placebo tablets at the same dosing schedule
Outcomes	Change in manual muscle testing, North Star Ambulatory Assessment scale, 6MWT and FVC. Molecular analyses included *SMN2* gene copy number, SMN2 transcript and SMN protein levels.
Notes	Study completed, but results are awaiting. Unknown date of completion; last update received March 2012 on WHO International Clinical trials Registry Platform.

NCT00568802

Methods	Randomised, placebo-controlled, double-blind trial
Participants	Participants with SMA types II and III, aged 1–10 years
Interventions	Hydroxyurea (dose and route) or placebo Duration of treatment: not mentioned
Outcomes	Motor function (Gross Motor Function Measure and timed motor tests), adverse events, pulmonary function, motor unit number estimation, SMN protein and SMN mRNA
Notes	Study completed, not enough data or results available for analysis or inclusion (or both). Unknown date of completion, last date received 2008.

NCT01645787

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	12 participants with SMA type III, aged 18–50 years
Interventions	4-AP 10 mg twice daily or placebo twice daily

NCT01645787 *(Continued)*

	Short-term treatment trial in which participants are treated for 2 weeks with 4-AP and placebo in random sequence followed by a long treatment trial of 6 weeks in which participants are also treated with placebo and 4-AP.
Outcomes	6MWT, Hammersmith Functional Motor Scale Expanded, manual muscle testing, change in motor unit estimation and nerve conduction studies
Notes	Study completed (September 2015), but no results available yet.

NCT02644668

Methods	Phase II, randomised, double-blind, placebo-controlled, 2 dose cohorts
Participants	72 participants, aged ≥ 12 years with genetically confirmed diagnosis of SMA and clinically SMA types II, III or IV
Interventions	Cohort 1: 36 participants with SMA type II, III or IV randomised 2:1 to CK-2127107 150 mg or placebo. Cohort 2: 36 participants with SMA type II, III or IV randomised 2:1 to CK-2127107 450 mg (or lower) or placebo. Both cohorts were also divided into 18 ambulatory versus 18 non-ambulatory participants.
Outcomes	Change from baseline and slope of change from baseline in FVC, MIP, MEP, HHD, HFMSE, RULM, TUG, 6MWT, and safety and tolerability measurements
Notes	Study completed (May 2018), but no results are available yet.

SPACE

Methods	Phase II, randomised, double-blind, placebo-controlled cross-over trial
Participants	45 participants with SMA types II, III and IV, aged ≥ 12 years
Interventions	Oral pyridostigmine (days 1–3: 2 mg/kg/day over 4 doses per day; days 4–7: 4 mg/kg/day over 4 doses per day; weeks 2–8: 6 mg/kg/day over 5 doses per day) or oral placebo (days 1–3: 2 mg/kg/day over 4 doses per day; days 4–7: 4 mg/kg/day over 4 doses per day; weeks 2–8: 6 mg/kg/day over 5 doses per day). Cross-over took place after 8 weeks with 1 week of washout.
Outcomes	Change in time to complete repeated 9 hole peg test, change in MFM scores, change in time to complete shuttle walk test, time to complete shuttle box and block test, change in pulmonary function (FVC), change in SMAFRS, change in PedsQL, fatigue and fatigability questionnaires, VAS scores, change in CMAP, and change in decremental response during repetitive nerve stimulation.
Notes	Study completed (January 2018), but no results are available yet.

4-AP: 4-aminopyridine; 6MWT: 6-minute walk test; CMAP: compound muscle action potential; FVC: forced vital capacity; HFMS(E): Hammersmith Functional Motor Scale (Expanded); HHD: hand-held dynamometry; MFM: Motor Function Measure; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; PedsQL: Pediatric Quality of Life Inventory; RULM: Revised Upper Limb Module; TUG: Time Up and Go; RULM; Revised Upper Limb Module; SMA: spinal muscular atrophy; SMN: survival motor neuron; SMAFRS: Spinal Muscular Atrophy Functional Rating Scale; TUG: Timed Up and Go; VAS: visual analogue scale; WHO: World Health Organization.

Characteristics of ongoing studies *[ordered by study ID]*

EMBRACE 2015

Trial name or title	A phase II, randomised, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of IONIS 396443 (BIIB058) administered intrathecally in subjects with spinal muscular atrophy who are not eligible to participate in the clinical studies IONIS 396443-CS3B or IONIS 396443-CS4
Methods	Phase II, randomised, double-blind, sham-procedure-controlled study
Participants	21 participants with genetically confirmed SMA with onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age and have documentation of 3 *SMN2* copies OR onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age, > 7 months of age (211 days) at screening, and have documentation of 2 *SMN2* copies OR onset of clinical signs and symptoms consistent with SMA at > 6 months of age, are ≤ 18 months of age at screening, and have documentation of 2 or 3 *SMN2* copies
Interventions	Multiple intrathecal injection of nusinersen (also called IONIS-SMN Rx or IONIS 396443) or multiple sham procedure with placebo
Outcomes	Number of adverse events and serious adverse events, change from baseline in clinical laboratory parameters, change from baseline in electrocardiogram, change from baseline in vital signs, change from baseline in neurological examination including motor function, change in plasma concentration of nusinersen and change in cerebrospinal fluid concentration of nusinersen
Starting date	June 2015
Contact information	Biogen
Notes	Study ongoing, but not recruiting participants.

NCT01671384

Trial name or title	Randomised placebo-controlled trial of valproic acid and levocarnitine in children with spinal muscular atrophy aged 2–15 years
Methods	Randomised, double-blind, placebo-controlled trial
Participants	60 participants with SMA types II or III, aged 2–15 years at time of inclusion Diagnosis of SMA has been made by the presence of exon7 deletion of *SMNT* gene OR by normal/mildly elevated creatine phosphokinase with electrodiagnostic characteristics suggestive of neurogenic weakness, normal motor and sensory nerve conduction velocities and muscle biopsy showing neurogenic atrophy or evidence of reinnervation (or both)
Interventions	Valproic acid (dose unknown) and levocarnitine 50 mg/kg/day (maximum 1000 mg) divided over 2 doses combined with physiotherapy or placebo combined with physiotherapy
Outcomes	Change in muscle strength (MMT on a 5-point scale), change in modified HFMS, change in FVC, adverse effects, changes in haematology, liver function and valproic acid levels
Starting date	August 2013 Estimated completion date December 2016
Contact information	G Sheffali, MD, Additional Professor

NCT01671384 *(Continued)*

	Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India
Notes	Study ongoing and recruiting participants

SMART02

Trial name or title	Multicenter cooperative and investigator initiated clinical trial using valproic acid in childhood onset spinal muscular atrophy: confirmatory trial (SMART02)
Methods	Phase IIB, randomised, double-blind, placebo-controlled trial
Participants	28 participants with SMA types I and II, aged 1–7 years
Interventions	Oral valproic acid or placebo, 12.5 mg/kg or 25 mg/kg once a day after supper. Treatment period: 40 weeks
Outcomes	HFMSE, HFMS, motor function, WHO motor milestones
Starting date	January 2016
Contact information	Kayoko Saito, Institute of Medical Genetics, Tokyo Women's Medical University, Japan
Notes	Study ongoing and recruiting participants

SUNFISH 2016

Trial name or title	A study to Investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in type 2 and 3 spinal muscular atrophy (SMA) participants (SUNFISH)
Methods	Randomised, placebo-controlled, double-blind trial
Participants	186 participants with SMA types II and III, aged 2–25 years old with a confirmed diagnosis of 5q-autosomal-recessive SMA
Interventions	Participants start with treatment in part 1 of the study: Part 1A includes adolescents and adults (aged 12–25 years) with SMA type II or III, ambulatory or non-ambulatory, receiving 12 weeks of placebo or RO7034067 Part 1B: children with SMA type II or III (aged 2–11 years), ambulatory or non-ambulatory, receiving 12 weeks of placebo or RO7034067 After 12 weeks of treatment, participants can participate in part 2 of the trial if they meet inclusion criteria. Part 2: participants aged 2–25 years with SMA type II or III, non-ambulatory with RULM entry item 1A ≥ 2 who have the ability to sit independently as assessed by item 9 of the MFM. 1 group will start with 12 months of placebo and will switch to treatment with RO7034067. 1 group will be treated for 24 months with RO7034067. All participants in part 2 will be offered the opportunity to enter an open-label extended phase after completing part 2.
Outcomes	Safety (incidence of adverse events), pharmacokinetics (plasma concentrations of RO6885247 and RO6885247 exposure), pharmacodynamics (SMN protein levels in blood and in vivo splicing of SMN2 mRNA in blood), change from baseline in motor scores (MFM-32, HFMSE, RULM), change from

SUNFISH 2016 *(Continued)*	baseline in pulmonary function (FVC, SNIP, FEV_1, peak cough flow), change from baseline in quality of life (PedsQL) and (severe) adverse events
Starting date	October 2016
Contact information	Hoffmann-La Roche
Notes	Study ongoing and recruiting participants

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HFMS(E): Hammersmith Functional Motor Scale (Expanded); MFM: Motor Function Measure; MMT: manual muscle testing; mRNA: messenger ribonucleic acid; PedsQL: Pediatric Quality of Life Inventory; RULUM: Revised Upper Limb Module; SNIP: sniff nasal inspiratory pressure; RULM; Revised Upper Limb Module; SMA: spinal muscular atrophy; WHO: World Health Organization.

ADDITIONAL TABLES

Table 1. Diagnostic criteria for SMA types II and III

Primary criteria
SMA type II: age of onset between 6 and 18 months and have been able to sit independently, but never been able to walk without assistance.
SMA type III: age of onset after 18 months and has/had the ability to walk without assistance.
Genetic analysis to confirm the diagnosis, with deletion or mutation of the SMN1 gene (5q11.2-13.3)
Supporting criteria
Symmetrical muscle weakness of limb and trunk.
Proximal muscles more affected than distal muscles and lower limbs more than upper limbs.
No abnormality of sensory function.
Serum creatine kinase activity ≤ 5 times the upper limit of normal
Denervation on electrophysiological examination, and no nerve conduction velocities < 70% of the lower limit of normal. No abnormal sensory nerve action potentials.
Muscle biopsy showing atrophic fibres of both types, hypertrophic fibres of one type (usually type I), and in chronic cases type grouping.
No involvement of the central neurological systems, such as hearing or vision.

Zerres 1999

Table 2. Oral creatine versus placebo outcomes (Wong 2007)

	Creatine	Placebo	Difference (95% CI)	P value
All ages				

Table 2. Oral creatine versus placebo outcomes (Wong 2007) *(Continued)*

Number of participants randomised	27	28	—	—
Number (%) of participants evaluable for analysis disability	18 (67%)	22 (79%)	—	—
Median change in disability score (GMFM)	0	-1	1 (-1 to 2)	0.19
Number (%) of participants evaluable for analysis QoL	17 (63%)	21 (75%)	—	—
Median change in quality of life (PedsQL, neuromuscular module)	-5	2	-7 (-11 to 3)	0.31
Age 2 to 5 years				
Number of participants randomised	8	12	—	—
Number (%) of participants evaluable for analysis disability	7 (88%)	10 (83%)	—	—
Median change in disability score (GMFM)	1	-2	1.5 (-4 to 9)	0.18
Number (%) of participants evaluable for analysis QoL	6 (75%)	9 (75%)	—	—
Median change in QoL (PedsQL, neuromuscular module)	4.5	3	2 (-8 to 13)	0.71
Age 5 to 18 years				
Number of participants randomised	19	16	—	—
Number (%) of participants evaluable for analysis disability and QoL	11 (58%)	12 (75%)	—	—
Median change in disability score (GMFM)	-1	-0.5	0 (-2 to 2)	0.77
Number (%) of participants evaluable for analysis QoL	11 (58%)	12 (75%)	—	—
Median change in quality of life (PedsQL, neuromuscular module)	-6	0	-6 (-15 to 2)	0.11
Number (%) of participants evaluable for analysis of muscle strength	11 (58%)	11 (69%)	—	—
Mean (SD) change in arms muscle strength (QMT)	-0.34 (6.98)	1.49 (8.50)	-1.83 (-8.75 to 5.09)	0.59
Mean (SD) change in legs muscle strength (QMT)	1.51 (4.21)	0.93 (3.06)	0.58 (-2.70 to 3.85)	0.72
Mean (SD) change in total muscle strength (QMT)	1.17 (9.67)	2.42 (10.3)	-1.25 (-10.1 to 7.6)	0.77
Number (%) of participants evaluable for analysis pulmonary function	11 (58%)	12 (75%)	—	—
Mean (SD) change in pulmonary function (FVC % of predicted value in litres)	-0.27 (14.5)	-0.83 (11.5)	0.56 (-10.75 to 11.87)	0.92
	Creatine	**Placebo**	**Risk ratio (95% CI)**	**P value**
All ages				
Number of adverse events	55	43	—	—

Table 2. Oral creatine versus placebo outcomes (Wong 2007) *(Continued)*

Number of participants with adverse events	13/27	16/28	0.84 (0.51 to 1.40)	0.59
Number of severe adverse events	NA	NA	—	—
Number of participants with severe adverse events	NA	1 (death by respiratory failure)	—	—

CI: confidence interval; FVC: forced vital capacity; GMFM: Gross Motor Function Measure; NA: not available; PedsQL: Pediatric Quality of Life Inventory; QMT: quantitative muscle test; QoL: quality of life; SD: standard deviation.

Table 3. Oral gabapentin versus placebo outcomes (Miller 2001a)

	Gabapentin	Placebo	Difference (95% CI)	P value
Follow-up at 12 months				
Number (%) of participants evaluable for analysis disability	32 (80%)	34 (77%)	—	—
Median change in disability score (SMAFRS)	0	-2	1 (-1 to 4)	0.30
Number (%) of participants evaluable for analysis quality of life	33 (83%)	34 (77%)	—	—
Mean change in quality of life (mini-SIP)	0.09	-0.26	0.36 (-0.29 to 1)	0.28
Number (%) of participants evaluable for analysis grip muscle strength	30 (75%)	31 (70%)	—	—
Mean change in grip muscle strength (MVC) in percentage from baseline	0.08	-4.5	4.6 (-2.5 to 11.6)	0.57
Number (%) of participants evaluable for analysis arms muscle strength	28 (70%)	29 (66%)	—	—
Mean change in arms muscle strength (MVC) in percentage from baseline	0.05	-1.8	1.9 (-2.5 to 6.2)	0.39
Number (%) of participants evaluable for analysis feet muscle strength	28 (70%)	29 (66%)	—	—
Mean change in feet muscle strength (MVC) in percentage from baseline	0.36	0.70	0.29 (-8.3 to 8.9)	0.95
Number (%) of participants evaluable for analysis total muscle strength	25 (63%)	25 (57%)	—	—
Mean change in total muscle strength (MVC) in percentage from baseline	1.2	-2.2	3.3 (-6.9 to 14)	0.52
Number (%) of participants evaluable for analysis development of walking	38 (95%)	35 (80%)	—	—
Number of participants with development of walking	0	0	—	—
Number (%) of participants evaluable for analysis pulmonary function	31 (78%)	34 (77%)	—	—

Table 3. Oral gabapentin versus placebo outcomes (Miller 2001a) *(Continued)*

Mean change in pulmonary function (FVC % of predicted value)	-4.0	-2.9	-1.1 (-4.1 to 1.9)	0.48

	Gabapentin	Placebo	Risk ratio (95% CI)	P value
Number of adverse events	NA	NA	—	—
Number of participants with adverse events	NA	NA	—	—
Number of severe adverse events	0	0	—	—
Number of participants with severe adverse events	0	0	—	—

CI: confidence interval; FVC: forced vital capacity; mini-SIP: mini Sickness Impact Profile; MVC: maximum voluntary contraction; NA: not available; SMAFRS: Spinal Muscular Atrophy-Functional Rating Scale.

Table 4. Oral hydroxyurea versus placebo outcomes (Chen 2010)

	Hydroxyurea	Placebo	Difference (95% CI)	P value
All ages				
Number of participants randomised	37	20	—	—
Number (%) of participants evaluable for analysis disability (GMFM)	37 (100%)	20 (100%)	—	—
Mean change (SE) in disability score (GMFM)	0.14 (0.57)	2.02 (0.88)	-1.88 (-3.89 to 0.13)	0.07
Number (%) of participants evaluable for analysis muscle strength (MMT)	37 (100%)	20 (100%)	—	—
Mean change (SE) in muscle strength (MMT)	-0.58 (0.56)	-0.03 (0.98)	-0.55 (-2.65 to 1.55)	0.60
Number (%) of participants evaluable for pulmonary function (FVC in litres)	37 (100%)	20 (100%)	—	—
Mean (SE) change in pulmonary function (FVC in litres)	-0.21 (0.06)	-0.22 (0.12)	-0.01 (-0.25 to 0.26)	0.93
Number (%) of participants evaluable for analysis disability (MHFMS)	26 (100%)	12 (100%)	—	—
Mean change (SE) in disability score (MHFMS)	0.02 (0.03)	0.04 (0.04)	-0.02 (-0.12 to 0.07)	0.70

	Hydroxyurea	Placebo	Risk ratio (95% CI)	P value
Number of adverse event episodes	224	129	—	0.65
Mean number (SD) of adverse event episodes per participant	6.05 (3.43)	6.45 (2.91)	-0.4 (-2.21 to 1.41)	0.66

Table 4. Oral hydroxyurea versus placebo outcomes (Chen 2010) *(Continued)*

Number of severe adverse event episodes	19	10	—	0.96
Mean number (SD) of severe adverse event episodes per participant	0.51 (1.04)	0.50 (0.83)	0.01 (-0.77 to 0.79)	0.96
Number (%) of participants discontinued intervention	2 (5%)	0 (0%)	—	—

FVC: forced vital capacity; GMFM: Gross Motor Function Measure; MHFMS: Modified Hammersmith Functional Motor Scale; MMT: manual muscle testing; SD: standard deviation; SE: standard error.

Table 5. Intrathecal injected nusinersen versus placebo outcomes (Mercuri 2018)

	Nusinersen	**Placebo**	**Difference (95% CI)**	**P value**
Number of participants randomised	84	42	—	—
Interim analysis[a]	84[b]	42[b]	—	—
Mean change in HFMSE	4.0	-1.9	5.9 (3.7 to 8.1)	< 0.001
Final analysis	84[c]	42[c]	—	—
Mean change in HFMSE	3.9	-1.0	4.9 (3.1 to 6.7)	—
	Nusinersen	**Placebo**	**Difference (95% CI)**	**P value**
Percentage of participants with 3-point-change on HFMSE (%)	57	26	30.5 (12.7 to 48.3)	< 0.001
Percentage (number) of children who achieved ≥ 1 new WHO motor milestone (% (number))	20 (13)	6 (2)	14 (-7 to 34)	0.08
	Nusinersen	**Placebo**	**Risk ratio (95% CI)**	**P value**
Percentage (number) of children who achieved ability to stand alone	2 (1)	3 (1)	0.5 (0.03 to 7.80)	—
Percentage (number) of children who achieved ability to walk with assistance	2 (1)	0 (0)	1.5 (0.06 to 36.1)	—
Number of participants with adverse events	78	42	0.9 (0.9 to 1.0)	0.01

CI: confidence interval; HFMSE: Hammersmith Functional Motor Scale Expanded; WHO: World Health Organization.

[a] Conducted in children who completed at least six months of the trial. Data of children who had not yet completed the 15-month period were imputed.

[b] Included 35 participants in the nusinersen group and 19 participants in the control group who completed the 15-month assessment. Data for 49 participants in the nusinersen group and 23 participants in the control group were imputed.

[c] The number of children with observed data for the 15-month assessment was 66 in the nusinersen group and 34 in the control group, and the number of children with imputed data was 18 in the nusinersen group and eight in the control group.

Table 6. Oral olesoxime versus placebo outcomes (Bertini 2017)

	Olesoxime	Placebo	Estimated difference (95% CI)[a]	P value
Number of participants randomised	108	57	—	—
Number (%) of participants evaluable for analysis MFM-32 D1+D2	103 (95%)	57 (100%)	—	—
Mean[ab] change (95% CI) in disability score (MFM D1+D2) at 24 months	-0.18 (-1.30 to 1.66)	-1.82 (-3.68 to 0.04)	2.00 (-0.25 to 4.25)	0.07
Number (%) of participants evaluable for analysis MFM total score	103 (95%)	57 (100%)	—	—
Mean[ab] change (95% CI) in disability score (MFM total score) at 24 months	0.59 (-0.9 to 2.070	-1.45 (-3.31 to 0.41)	2.04 (-0.21 to 4.28)	0.08
Number (%) of participants evaluable for analysis HFMS	103 (95%)	57 (100%)	—	—
Mean[b] change (95% CI) in disability score (HFMS) at 24 months	-0.78 (-1.60 to 0.04)	-1.72 (-2.74 to -0.70)	0.94 (-0.28 to 2.17)	0.13
Number (%) of participants evaluable for analysis of nerve innervation value (CMAP) (in mV)	70 (65%)	34 (60%)	—	—
Mean[b] (95% CI) change in total amplitude CMAP from baseline to 24 months	-0.07 (-0.49 to 0.36)	-0.16 (-0.74 to 0.43)	NA	0.79
Number (%) of participants evaluable for analysis of MUNE	58 (54%)	30 (53%)	—	—
Mean[b] (95% CI) change in total MUNE from baseline to 24 months	-4.51 (-12.21 to 3.18)	-6.69 (-16.86 to 3.48)	NA	0.71
Number (%) of participants evaluable for FVC	64 (59%)	38 (67%)	—	—
Mean[b] (95% CI) change in FVC from baseline to 24 months	4.28 (-0.32 to 8.88)	6.16 (1.00 to 11.33)	-1.88 (-3.14 to 6.91)	0.57
	Olesoxime	**Placebo**	**Difference (95% CI)**	**P value**
Number (%) of participants evaluable for analysis of quality of life (Ped-sQL) from baseline to 24 months	71 (66%)	37 (65%)	—	—
Mean (SD) change in quality of life (PedsQL) from baseline to 24 months	NA	NA	0.25 (-4.58 to 5.08)	0.92
	Olesoxime	**Placebo**	**Risk ratio (95% CI)**	**P value**
Number (%) of participants evaluable for responder analysis MFM-32 score D1+D2 (24 months)	103 (95%)	57 (100%)	—	—
Proportion of participants with good response according to MFM-32 score D1+D2[c]	56 (54)	22 (39)	1.43 (-0.98 to 2.08)	0.06
Number of adverse events	1104 (64)	612 (36)	—	—

Table 6. Oral olesoxime versus placebo outcomes (Bertini 2017) *(Continued)*

Number (%) of participants with adverse events	103 (95%)	57 (100%)	0.95 (0.91 to 0.99)	0.02
Number (%) of participants with severe adverse events	18 (17%)	14 (25%)	0.67 (0.37 to 1.26)	—
Number of deaths	1	1	—	—
Number (%) of participants discontinued intervention	10 (9%)	7 (12%)	—	—

CI: confidence interval; CMAP: compound muscle action potential; FVC: forced vital capacity; HFMS: Hammersmith Functional Motor Scale; MFM: Motor Function Measure; MFM D1+D2: functional domains 1 and 2 of the Motor Function Measure; MUNE: motor unit number estimation; NA: not available; PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation.

[a] Least squared mean of MFM, including MFM-32 and MFM-20 assessments.

[b] Calculated with available data.

[c] Participants with no change or improvement of scores were considered 'responders', participants with a decline in score were considered 'non-responders'.

Table 7. Oral phenylbutyrate versus placebo outcomes (Mercuri 2007)

	Phenylbutyrate	Placebo	Difference (95% CI)	P value
All ages				
Number of participants randomised	54	53	—	—
Number (%) of participants evaluable for analysis of HFMS	45 (83%)	45 (85%)	—	—
Mean (SD) HFMS	12.1 (9.60)	12.8 (9.86)	-0.7 (-4.78 to 3.78)	0.70
Mean (SD) change in HFMS[a]	0.60 (0.22)	0.73 (0.29)	-0.13 (-0.84 to 0.58)	0.70
Age > 5 years				
Mean (SD) change in muscle strength arm megascore (dynamometry)[a]	1.56 (6.94)	-0.42 (8.61)	1.98 (-1.67 to 5.63)	0.74
Mean (SD) change muscle strength leg megascore (dynamometry)[a]	4.26 (8.64)	3.22 (6.26)	1.04 (-2.46 to 4.54)	0.78
Number (%) of participants evaluable for analysis of HFMS	26 (48%)	23 (43%)	—	—
Mean (SD) change in pulmonary function (FVC % of predicted value in litres)[a]	0.03 (0.17)	-0.01 (0.27)	0.04 (-0.07 to 0.15)	0.39
	Phenylbutyrate	**Placebo**	**Risk ratio (95% CI)**	**P value**
All ages				
Number of participants with adverse events	19	5	3.1 (1.25 to 7.84)	0.01
Number of withdrawals because of adverse events	6	3	1.86 (0.49 to 7.11)	0.9

Table 7. Oral phenylbutyrate versus placebo outcomes (Mercuri 2007) *(Continued)*

Number of severe adverse events	1	2	—	—
Number of participants with severe adverse events	1	2	1.96 (0.18 to 21.0)	1.0

CI: confidence interval; FVC: forced vital capacity; HFMS: Hammersmith Functional Motor Scale; SD: standard deviation;
[a]Mean change from baseline.

Table 8. Subcutaneous somatotropin versus placebo outcomes (Kirschner 2014)

Total number of participants randomised (cross-over setting)	20		—	—
	Somat-ropin	**Placebo**	**Difference (95% CI)**	**P value**
Number of participants completing phase 1 of study protocol	9/10	10/10	—	—
Number of participants completing phase 2 of study protocol	8/10	9/10	—	—
Number (%) of participants evaluable for intention-to-treat analysis	17 (90%)	17 (80%)	—	—
Mean (SD) change in muscle strength of upper limb (hand-held myometry in megascore of biceps and handgrip) (Newton)	-1.05 (6.42)	0.30 (10.6)	-1.35 (-7.12 to 4.42)	0.97
Number (%) of participants evaluable for analysis disability score (HFMSE)	19 (95%)	19 (95%)	—	—
Median (SD) change in disability score (HFMSE)	0.05 (3.19)	-1.05 (5.28)	0.25 (-1 to 2.5)	0.58
Number (%) of participants evaluable for analysis arm megascore	19 (95%)	19 (95%)	—	—
Mean (SD; range) change in arm megascore (Newton)	-1.05 (6.42; -11 to 19)	0.30 (10.60; -18 to 34.3)	0.08 (-3.79 to 3.95)	0.97
Number (%) of participants evaluable for analysis leg megascore	19 (95%)	19 (95%)	—	—
Mean (SD; range) change in leg megascore (Newton)	2.96 (7.64; -10 to 24.5)	0.95 (9.93; -18 to 22)	2.23 (-2.19 to 6.63)	0.30
Number (%) of participants evaluable for analysis muscle strength (MRC)	19 (95%)	19 (95%)	—	—
Mean (SD) change MRC (% of maximum score)	-2.31 (5.1)	0.43 (7.0)	-2.74 (-6.7 to 1.29)	0.19
Number (%) of participants evaluable for analysis pulmonary function (FVC)	19 (95%)	19 (95%)	—	—
Mean (SD; range) change in pulmonary function (FVC improvement in litres)	0.12 (0.25; -0.4 to 0.5)	-0.11 (0.40; -1.4 to 0.36)	0.23 (-0.01 to 0.45)	0.08
	Somat-ropin	**Placebo**	**Risk Ratio (95% CI)**	**P value**
Number of adverse events	14	9	—	—

Table 8. Subcutaneous somatotropin versus placebo outcomes (Kirschner 2014) *(Continued)*

Number of participants with adverse events	11	7	1.57 (0.78 to 3.17)	0.34
Number (%) of participants discontinued intervention	3 (15%)	0 (0%)	—	—

CI: confidence interval; FVC: forced vital capacity; HFMSE: Hammersmith Functional Motor Scale Expanded; MRC: Medical Research Council; SD: standard deviation.

Table 9. Intravenous TRH versus placebo outcomes (Tzeng 2000)

	TRH	Placebo	Difference (95% CI)
Number of participants randomised	6	3	—
Number (%) of participants evaluable for analysis	6 (100%)	3 (100%)	—
Mean (SD) change in muscle strength (dynamometry in pounds)	0.82 (0.59)	0.48 (0.29)	0.34 (-0.54 to 1.22)
	TRH	**Placebo**	**Risk ratio (95% CI)**
Number of adverse events	12	0	—
Number of participants with adverse events	NA	NA	—
Number of severe adverse events	0	0	—
Number of participants with severe adverse events	0	0	—

CI: confidence interval; NA: not available; SD: standard deviation; TRH: thyrotropin-releasing hormone.

Table 10. Oral valproic acid plus acetylcarnitine versus placebo outcomes (Swoboda 2010)

	Valproic acid + acetyl-L-carnitine	Placebo	Difference (95% CI)	P value
All ages				
Number of participants randomised	31	30	—	—
Number (%) of participants evaluable for analysis disability (MHFMS)	28 (90%)	28 (93%)	—	—
Mean change (SD) in disability score (MHFSM) at 6 months	0.82 (2.88)	0.18 (3.98)	0.64 (-1.1 to 2.38)	0.50
Number (%) of participants evaluable for analysis of nerve innervation value (CMAP)	19 (61%)	19 (63%)	—	—
Mean (SD) change in total amplitude CMAP from baseline to 6 months	0.02 (0.70)	-0.10 (0.66)	0.12 (-0.33 to 0.57)	0.59

Table 10. Oral valproic acid plus acetylcarnitine versus placebo outcomes (Swoboda 2010) *(Continued)*

Number (%) of participants evaluable for analysis of quality of life (PedsQL) from baseline to 12 months	27 (87%)	27 (90%)	—	—
Mean (SD) change in quality of life (PedsQL) from baseline to 12 months	-1.9 (13.6)	0.3 (12.9)	-2.2 (-9.27 to 4.87)	0.54
Age < 3 years old				
Number (%) of participants evaluable for analysis disability (MHFMS)	12 (52%)	11 (48%)	—	—
Mean change (SD) in disability score (MHFSM) from baseline to 6 months	1.33 (2.27)	1.09 (5.37)	0.24 (-3.28 to 3.76)	0.89
Aged 3–8 years				
Number (%) of participants evaluable for analysis disability (MHFSM)	18 (47%)	17 (45%)	—	—
Mean change (SD) in disability score (MHFSM) from baseline to 6 months	0.44 (3.29)	-0.41 (2.79)	0.85 (-1.25 to 2.95)	0.42
Aged ≥ 5 years				
Number of participants evaluable for analysis muscle strength in arms (myometry)	7	7	—	—
Mean (SD) change in arm muscle strength (myometry) from baseline to 6 months (kg)	0.64 (0.6)	0.07 (1.04)	0.57 (-0.45 to 1.58)	0.23[a]
Number of participants evaluable for analysis muscle strength in legs (myometry)	6	4	—	—
Mean (SD) change in leg muscle strength (myometry) from baseline to 6 months (kg)	0.55 (0.83)	-0.85 (2.22)	1.40 (-1.98 to 4.79)	0.19[a]
Number of participants evaluable for analysis muscle strength in both arms and legs (myometry)	7	8	—	—
Mean (SD) change in total muscle strength (myometry) from baseline to 6 months (kg)	1.18 (0.91)	-0.25 (2.47)	1.43 (0.69 to 3.56)	0.21
Number of participants evaluable for analysis pulmonary function (FVC in % of predicted)	NA	NA	NA[a]	NA[a]
Mean (SD) change in pulmonary function (FVC in % of predicted) from baseline to 6 months	NA	NA	—	—
	Valproic acid + acetyl-L-carnitine	**Placebo**	**Risk ratio (95% CI)**	**P value**
All ages				
Number (%) of participants with adverse events (6 months)	23 (77%)	18 (58%)	1.32 (0.92 to 1.89)	—

Table 10. Oral valproic acid plus acetylcarnitine versus placebo outcomes (Swoboda 2010) *(Continued)*

Number (%) of participants with severe adverse events (6 months)	6 (20%)	2 (6%)	3.1 (0.60 to 12.1)	—

CI: confidence interval; CMAP: compound maximum action potential; FVC: forced vital capacity; MHFMS: Modified Hammersmith Functional Motor Scale; PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation.
[a] Underpowered.

Table 11. Oral valproic acid versus placebo outcomes (Kissel 2014)

	Valproic acid	Placebo	Difference (95% CI)[a]	P value
Number (%) of participants randomised first 6 months (cross-over setting)	16 (100%)	17 (100%)	—	—
Number (%) of participants evaluable for analysis after 12 months	30 (91%)	30 (91%)	—	—
Analysis after 6 months before cross-over				
Number (%) of participants evaluable for analysis SMAFRS	14 (88%)	17 (100%)	—	—
Mean (SD) change in SMAFRS	-0.29 (1.59)	-0.35 (2.32)	0.06 (-1.32 to 1.44)	0.93
Number (%) of participants evaluable for analysis upper extremity	14	16	—	—
Mean (SD) change in MVICT upper extremity (Newton)	-0.24 (1.17)	-0.01 (1.05)	-0.23 (-1.03 to 0.57)	0.54
Number (%) of participants evaluable for analysis lower extremity	13	16	—	—
Mean (SD) change in lower extremity MVICT (Newton)	-0.02 (0.65)	0.35 (1.30)	-0.37 (-1.09 to 0.35)	0.36
Number (%) of participants evaluable for analysis pulmonary function (FVC)	14 (88%)	17 (100%)	—	—
Mean (SD; range) change in pulmonary function (FVC improvement in litres)	-0.04 (0.35)	0.30 (1.20)	-0.34 (-0.94 to 0.26)	0.31
Number of participants evaluable for QoL analysis	14	17	—	—
Mean (SD) change in mini-SIP for QoL	-0.19 (2.80)	0.91 (4.78)	-1.1 (-3.8 to 1.6)	0.53
	Valproic acid	**Placebo**	**Risk ratio (95% CI)[a]**	**P value**
Number of adverse events	30	66	—	—
Number of participants with adverse events	12	15	0.8 (0.44 to 1.44)	
Number of severe adverse events	2	3	—	—

Table 11. Oral valproic acid versus placebo outcomes (Kissel 2014) *(Continued)*

Number of participants with severe adverse events	2	2	1.0 (0.15 to 6.69)	—
Number (%) of participants discontinued intervention	NA	NA	—	—

CI: confidence interval; FVC: forced vital capacity; mini-SIP: mini-Sickness Illness Profile; MVICT: maximum voluntary isometric contraction; NA: not available; QoL: quality of life; SD: standard deviation; SMAFRS: Spinal Muscular Atrophy Functional Rating Scale.
[a]Calculated with available data.

APPENDICES

Appendix 1. SMN1 gene therapies

SMN1 gene therapy

Studies that aim to study the repair of the *SMN1* deletion by the introduction of the *SMN1* gene have started. Viral vectors, such as the self-complementary adeno-associated virus (scAAV9) are used to incorporate the *SMN1* gene. In vitro studies in fibroblasts of people with SMA (Azzouz 2004; Dominguez 2011), and in vivo studies in mice (Benkhelifa-Ziyyat 2013; Dominguez 2011), primates, and pigs with SMA phenotype have shown promising results on SMN1-expression with effect on motor function and survival (Duque 2015; Foust 2010; Glascock 2012a; Glascock 2012b; Passini 2011; Robbins 2014; Valori 2010). These studies also indicate that intramuscular or intravenous injection of the adeno-associated virus (AAV) results in widespread dissemination of the gene, including penetration of the central nervous system (Benkhelifa-Ziyyat 2013; Foust 2010; Glascock 2012a; Meyer 2015).

One phase I study with intravenous AVXS-101 (scAAV9.CB.SMN) in infants with SMA type I has been completed and showed all 15 participants to be alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. Participants included in the study also showed improvement on the CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; 0 to 66 scale) (increase of 9.8 points at one month and 15.4 points at three months, as compared with a decline in this score in a historical cohort) (Mendell 2016; Mendell 2017).

One phase I study with intrathecal AVXS-101 has started in 27 children with SMA type II aged six to 60 months testing three different doses (6.0×10^{13} vg or AVXS-101, 1.2×10^{13} vg of AVXS-101 or 2.4×10^{13} vg of AVXS-101) (STRONG).

Appendix 2. Other experimental factors studied in vivo and vitro

Several compounds have an effect on SMN expression in vivo and in vitro. These include 2,4-diaminoquinazolines (RG3039 and D156844) (Butchbach 2010; Gogliotti 2013; Jarecki 2005; Singh 2008; Thurmond 2008, van Meerbeke 2013), 2,4-diaminoquinazoline inhibitors of the decapping scavenger enzyme DcpS (DAQ-DcpSi) (Cherry 2017), 2-(4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl)-7-(4-methylpiperazin-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (Woll 2016), 3-(6,8-Dimethylimidazo[1,2-a]pyrazin-2-yl)-7-(4-methylpiperazin-1-yl)-1H-isochromen-1-one (Woll 2016), 4PBA (Butchbach 2016), 5-(N-ethyl-N-isopropyl)-amiloride (Yuo 2008), AAV8.LSP.dnMstn (Liu 2016), AAV8.LSP.sActRIIB (Liu 2016), aclarbicin (Andreassi 2004; Ting 2007), amikacin (Wolstencroft 2005), BAY 55-9837 (Hadwen 2014), bortezomib (Kwon 2011), butyrate prodrug pivaloyloxymethyl butyrate (AN9) (Edwards 2016), dacinostat (Mohseni 2016), $E1^{mov11}$ (Osman 2016), edavarone (Ando 2017); fasudil (Bowerman 2012), Genetics/G418 (Heier 2009; Heier 2015), Indoprofen (Lunn 2004), loganin (Tseng 2016), M344 (Riessland 2006), ML372 (Abera 2016), panobinostat/LBH589 (Garbes 2009), Pip6a-PMO (Hammond 2016), PTK-SMA1 (Hastings 2009), quercetin (Uzunalli 2015; Wishart 2014), quisinostat/JNJ-26481585 (Schreml 2013), romidepsin (Hauke 2009), scAAV9-siPTEN (Ning 2010; Little 2015), securinine (Chen 2017), SMN-AS1 (d'Ydewalle 2017; Woo 2017), sodium vanadate (Liu 2014; Ting 2007; Zhang 2001), suberoylanilide hydroxamic acid (Hahnen 2006; Mohseni 2016; Riessland 2010), TC007 (Mattis 2009a; Mattis 2009b; Mattis 2012), (S)-3-(6,8-dimethylimidazo[1,2-a]pyrazin-2-yl)-7-(4-ethyl-3-methylpiperazin-1-yl)-2H-chromen-2-one (Woll 2016), tobramycin (Wolstencroft 2005), trichostatin A (Avila 2007; Liu 2014; Ting 2007), triptolode (Hsu 2012), VK563 (Butchbach 2016), and Y-27632 (Bowerman 2010). Every compound has its own potential and way of interacting with the SMN complex. Description of the working mechanism of each compound goes behind the scope of this review, since none of the compounds have yet been investigated in human studies.

At the time of writing, it is unclear whether treatment with any of these drugs has a beneficial clinical effect on the disease course of SMA types II and III.

Appendix 3. Cochrane Neuromuscular Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Muscular Atrophy, Spinal Explore All [REFERENCE] [STANDARD]
#2 MeSH DESCRIPTOR Muscular Disorders, Atrophic [REFERENCE] [STANDARD]
#3 "spinal muscular" NEXT atroph* [REFERENCE] [STANDARD]

#4 Werdnig NEXT Hoffman* [REFERENCE] [STANDARD]
#5 Kugelberg next Welander [REFERENCE] [STANDARD]
#6 #1 or #2 or #3 or #4 or #5 [REFERENCE] [STANDARD]
#7 (#1 or #2 or #3 or #4 or #5) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 4. Cochrane Central Register of Controlled Trials (CENTRAL) (CRSO) search strategy

Search run on 22 October 2018

#1 MESH DESCRIPTOR Muscular Atrophy, Spinal EXPLODE ALL TREES 32
#2 Werdnig near Hoffman* 2
#3 Kugelberg near Welander 1
#4 spinal near muscul* near atroph* 66
#5 #1 or #2 or #3 or #4 72

Appendix 5. MEDLINE (OvidSP) search strategy

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1991 to Present> Ovid MEDLINE(R) 1946 to October week 43 2018

Search strategy:
---
1 randomized controlled trial.pt. (469833)
2 controlled clinical trial.pt. (95075)
3 randomized.ab. (405868)
4 placebo.ab. (192439)
5 drug therapy.fs. (2035863)
6 randomly.ab. (286433)
7 trial.ab. (428139)
8 groups.ab. (1764357)
9 or/1-8 (4191699)
10 exp animals/ not humans.sh. (4669484)
11 9 not 10 (3613302)
12 exp Muscular Atrophy, Spinal/ (4602)
13 muscular disorders, atrophic/ (426)
14 spinal muscular atroph$.mp. (4867)
15 (Werdnig adj Hoffman$).mp. (393)
16 (Kugelberg adj Welander).mp. (189)
17 or/12-16 (6876)
18 11 and 17 (709)
19 remove duplicates from 18 (604)
20 limit 19 to yr="1991 -Current" (539)

Appendix 6. Embase (OvidSP) search strategy

Database: Embase <1991 to 2018 week 43>
Search strategy:
---
1 crossover-procedure.sh. (54096)
2 double-blind procedure.sh. (137638)
3 single-blind procedure.sh. (27791)
4 randomized controlled trial.sh. (465768)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1349705)
6 trial.ti. (215268)
7 or/1-6 (1506890)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1735631)
9 animal/ or nonanimal/ or animal experiment/ (3746312)
10 9 not 8 (3037555)
11 7 not 10 (1393170)
12 spinal muscular atrophy/ or hereditary spinal muscular atrophy/ (6331)
13 (Werdnig adj Hoffman$).mp. (627)
14 (Kugelberg adj Welander).mp. (333)
15 spinal muscul$ atroph$.mp. (7028)
16 or/12-15 (7410)

17 11 and 16 (148)
18 limit 17 to yr="1991 -Current" (141)
19 remove duplicates from 18 (132)

Appendix 7. ISI Web of Science Conference Proceedings search strategy

WOS 22 October 2018
Indexes=CPCI-S, CPCI-SSH Timespan=1991-2018

#6 8 #5 AND #4
#5 211,588 TS=(random* or placebo or "single blind" or "double blind*" or crossover or "cross-over")
#4 543 #1 or #2 or #3
#3 3 TS=(Kugelberg AND Welander)
#2 14 TS=(Werdnig AND Hoffman*)
#1 536 TS=("muscular atrophy" NEAR spinal)

Appendix 8. ClinicalTrials.gov search strategy

1 spinal muscular atrophy

2 drug therapy OR treatment OR trial

Appendix 9. WHO International Clinical Trials Registry Platform search strategy

1 spinal muscular atrophy

2 SMA

WHAT'S NEW

Date	Event	Description
22 October 2018	New search has been performed	Protocol modification in primary and secondary outcomes. Protocol modification in SMA type. Transformation of disability scores into MRC scores has been removed, since it is not possible for the included study population. We revised the methods to conform to current Cochrane standards.
20 June 2017	New citation required and conclusions have changed	Updated search October 2018. Four new trials included. Inclusion of 'Summary of findings' tables. Re-evaluation of 'Risk of bias' assessments. One author (J Wokke) retired from authorship. Fay-Lynn Asselmann joined the author team.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 1, 2009

Date	Event	Description
15 February 2012	Amended	'Declaration of interest' and 'Contributions of authors' updated; no other changes to text.
15 February 2012	New citation required but conclusions have not changed	Change in listing of authors to include Dr WL van der Pol. This corrects an error in the authorship of this update.

Date	Event	Description
31 March 2011	New citation required but conclusions have not changed	RI Wadman included as new lead author.
8 March 2011	New search has been performed	Databases were searched and review was updated. Two new trials were found.
30 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All authors contributed substantially to the concept and design of the review.

WB and AV performed data extraction and analyses for the original review in 2009.

WB wrote the first draft of the original review and the other co-authors contributed to subsequent revisions for important intellectual content.

RW, AV and WP updated the review in 2011 and 2019 and the other authors approved the revisions.

DECLARATIONS OF INTEREST

RW: was involved as investigator at a participating centre in the trials on the safety and efficacy of cholest-4-en-3-one, oxime for children with SMA types II and IIIa (Bertini 2017; OLEOS), and is involved as an investigator in the monocentre placebo-controlled trial of pyridostigmine in children and adults with SMA types II to IV (SPACE). She does not receive any funding from the pharmaceutical industry.

WP: receives research support from the Prinses Beatrix Spierfonds, Stichting Spieren voor Spieren, Netherlands ALS foundation. His employer receives fees for consultancy services to Biogen, Avexis and Novartis. WP was an investigator at a participating centre in the trials on the safety and efficacy of cholest-4-en-3-one, oxime for children with SMA types II and IIIa (Bertini 2017; OLEOS), and is an investigator in the monocentre placebo-controlled trial of pyridostigmine in children and adults with SMA types II to IV (SPACE).

WB: none.

FA: none.

LB: serves on scientific advisory boards for the Prinses Beatrix Spierfonds, Thierry Latran Foundation, Biogen Idec and Cytokinetics; received an educational grant from Baxter International Inc; serves on the editorial board of Amyotrophic Lateral Sclerosis and the Journal of Neurology, Neurosurgery and Psychiatry; and receives research support from the Prinses Beatrix Fonds, Netherlands ALS Foundation, The European Community's Health Seventh Framework Programme (grant agreement number 259867), and The Netherlands Organization for Health Research and Development (Vici Scheme, JPND (SOPHIA, STRENGTH)). LB was an investigator at a participating centre in the trials on the safety and efficacy of cholest-4-en-3-one, oxime for children with SMA types II and IIIa (Bertini 2017; OLEOS) and is an investigator of the monocentre placebo-controlled trial on pyridostigmine in children and adults with SMA types II to IV (SPACE).

SI: Dr Iannaccone was involved in the trial of riluzole as one of the investigators and authors (Russman 2003). She was involved in a trial of the efficacy of creatine for children with spinal muscular atrophy types II and III as investigator and author (Wong 2007) and she was involved in a trial of the efficacy of riluzole (not published). She has received support for research from AveXis, Biogen and Scholar Rock for clinical trials in SMA patients and from Sarepta, Reveragen, Mallinckrodt, Fibrogen, and PTC Therapeutics for clinical trials in muscular dystrophy. She has been a consultant for AveXis, Biogen, Sarepta, Audentes, Catabasis and Genentech/Roche.

AV: none known. He was involved as investigators at a participating centre in the trials on the safety and efficacy of cholest-4-en-3-one, oxime for children with SMA types II and IIIa (Bertini 2017; OLEOS), and is an investigator in the monocentre placebo-controlled trial of pyridostigmine in children and adults with SMA types II to IV (SPACE).

SOURCES OF SUPPORT

Internal sources

- University Medical Center Utrecht, Department of Neurology and Neuromuscular diseases, Utrecht, Netherlands.
- University Medical Center Utrecht, Department of Neurology, Utrecht, Netherlands.
- University Medical Center Utrecht, Department of Biostatics and Clinical Epidemiology, Utrecht, Netherlands.

- Cochrane Neuromuscular Disease Group, King's College London School of Medicine, London, UK.
- University of Texas Southwestern Medical Center, Department of Pediatrics, Dallas, Texas, USA.
- Onze Lieve Vrouwe Gasthuis West, Department of Neurology, Amsterdam, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The 'Risk of bias' methodology was revised in the first update according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We expanded the methods according to current standards in the 2017 update, as meta-analysis may be possible in future updates. We included 'Summary of findings' tables. We did not consider use of explicit inclusion and exclusion criteria or explicit outcome criteria as part of our 'Risk of bias' analysis as these considerations relate to indirectness of evidence, which is one of the GRADE criteria. We considered baseline imbalance in relation to allocation bias.

The search strategy was adjusted. Searches were performed from 1991 onwards because at that time genetic analysis of the *SMN1* gene became widely available and could be used to establish the diagnosis of SMA.

We adjusted the definition on SMA types II and III in Table 1 and added the highest achieved motor milestones (sitting, walking) as discriminators of the SMA types II and III. This was not stated in table 1 of original protocol and the update of 2011, although it was mentioned in the main text.

Change in forced vital capacity (FVC), as a percentage of FVC predicted for height, was added as a secondary outcome measure. This was not stated in the original protocol but many trials used this as a measure of pulmonary function or the strength of respiratory muscles. Transformation of disability scores into Medical Research Council scores has been removed in the update of 2019, since the transformation is not possible for the included study population and its clinical scores.

The 'Adverse events' section was revised and we did not discuss the adverse events from the included trials in relation to the adverse effects of drug treatment in non-randomised literature. We have outlined the most common adverse events of treatments in the 'Summary of findings' tables (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 10; Summary of findings 9).

RW joined the review for the 2011 update and FA joined this update. At the 2019 update, J Wokke retired from authorship.

We added some additional information to the methods to update them to current reporting standards and specify methods for any future meta-analysis We:

- clarified that we did not use outcomes for study selection;
- searched clinical trials registries to identify unpublished and ongoing studies;
- added a PRISMA flow chart to illustrate the study selection process;
- specified methods for use if studies with multiple eligible intervention arms are identified;
- specified rules of thumb levels for assessment of heterogeneity from Higgins 2011;
- specified use of random-effects model with a sensitivity analysis using a fixed-effect analysis, should meta-analysis be possible;
- stated that we would use standardised mean difference if different scales were used to measure the same construct;
- included 'Summary of findings' tables and the GRADE analysis according to Cochrane requirements.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetylcarnitine [therapeutic use]; Amines [therapeutic use]; Creatine [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Disease Progression; Gabapentin; Hydroxyurea [therapeutic use]; Neuroprotective Agents [*therapeutic use]; Phenylbutyrates [therapeutic use]; Randomized Controlled Trials as Topic; Spinal Muscular Atrophies of Childhood [*drug therapy]; Thyrotropin-Releasing Hormone [therapeutic use]; Valproic Acid [therapeutic use]; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans