Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-061-z Risdiplam

Stand: April 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Risdiplam [spinale Muskelatrophie] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Nusinersen: Beschluss vom 21. Dezember 2017
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Risdiplam Xxx Evrysdi	Anwendungsgebiet laut Zulassung: Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.
Nusinersen M09AX07 Spinraza	Behandlung der 5q-assoziierten spinalen Muskelatrophie
Onasemnogen-Abeparvovec M09AX Zolgensma	Behandlung von Patienten mit 5q-assoziierter spinaler Muskelatrophie (SMA) mit einer biallelischen Mutation im SMN1-Gen und einer klinisch diagnostizierten Typ-1-SMA, oder Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und bis zu 3 Kopien des SMN2-Gens.

Quellen: AMIce-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse Event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CHOPINTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HFMSE	Hammersmith Functional Motor Scale-Expanded
HINE	Hammersmith Infant Neurological Examination
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MCGRs	magnetically controlled growing rods surgery
MM	motor milestones
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
RSV	respiratory syncytial virus
SIGN	Scottish Intercollegiate Guidelines Network
SMA	Spinale Muskelatrophie
SMN	survival of motor neuron
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

5q-assoziierte spinale Muskelatrophie

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *spinale Muskelatrophie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.03.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 175 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [2].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Dezember 2017/16. Mai 2019 - Nusinersen.

Anwendungsgebiet

Spinraza wird zur Behandlung der 5q-assoziierten spinalen Muskelatrophie angewendet.

Zweckmäßige Vergleichstherapie

Nusinersen ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens.

Fazit / Ausmaß des Zusatznutzens

a) Für Patienten mit 5q-assoziierter spinaler Muskelatrophie (5q-SMA) Typ 1: Ausmaß des Zusatznutzens: Erheblich

b) Für Patienten mit 5q-SMA Typ 2: Ausmaß des Zusatznutzens: Beträchtlich

c) Für Patienten mit 5q-SMA Typ 3: Ausmaß des Zusatznutzens: Nicht quantifizierbar

d) Für Patienten mit 5q-SMA Typ 4: Ausmaß des Zusatznutzens: Nicht quantifizierbar

3.2 Cochrane Reviews

Wadman RI et al., 2020 [6].

Drug treatment for spinal muscular atrophy types II and III.

Fragestellung

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.

Methodik

Population:

- Children or adults with SMA types II and III

Intervention/Komparator:

- 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

Endpunkte:

- change in disability score within one year after the onset of treatment, 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

Recherche/Suchzeitraum:

- 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.

Qualitätsbewertung der Studien:

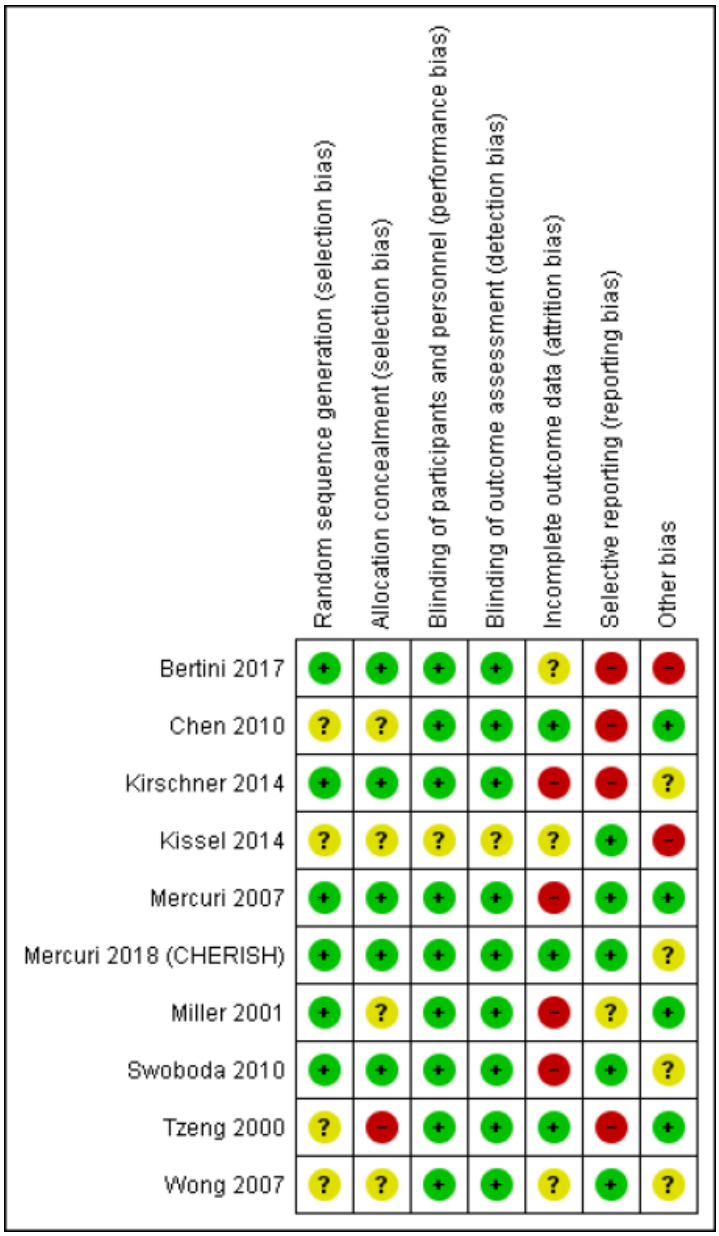
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 randomised, placebo-controlled trials with 717 participants. We added four of the trials at this update
- The trials investigated creatine (Wong 2007, 55 participants), gabapentin (Miller 2001, 84 participants), hydroxyurea (Chen 2010, 57 participants), nusinersen (Mercuri 2019 [CHERISH], 126 participants), olesoxime (Bertini 2017, 165 participants), phenylbutyrate (Mercuri 2017, 107 participants), somatotropin (Kirschner 2014, 20 participants), thyrotropin-releasing hormone (TRH) (Tzeng 2000, nine participants), valproic acid (Swoboda 2010, 33 participants), and combination therapy with valproic acid and acetyl-L-carnitine (ALC) (Kissel 2014, 61 participants). Treatment duration was from three to 24 months

Qualität der Studien:



Ergebnisse:

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 control group was –1.9 points	The mean change in HFMSE in the nusinersen-treated group was 5.9 points higher than in the sham procedure group (3.7 higher to 8.1 higher)	**MD 5.9** (3.7 to 8.1)	126 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	
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.

- 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.

Anmerkung/Fazit der Autoren

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.

Wadman RI et al., 2019 [5].

Drug treatment for spinal muscular atrophy type I.

Fragestellung

To assess the efficacy and safety of any drug therapy designed to slow or arrest progression of spinal muscular atrophy (SMA) type I.

Methodik

Population:

- Children with SMA type I

Intervention/Komparator:

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

Endpunkte:

- age at death or full-time ventilation, acquisition of motor milestones, i.e. head control, rolling, sitting or standing, motor milestone response on disability scores within one year

after the onset of treatment, and adverse events and serious adverse events attributable to treatment during the trial period

Recherche/Suchzeitraum:

- Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, EMBASE, and ISI Web of Science conference proceedings in October 2018

Qualitätsbewertung der Studien:

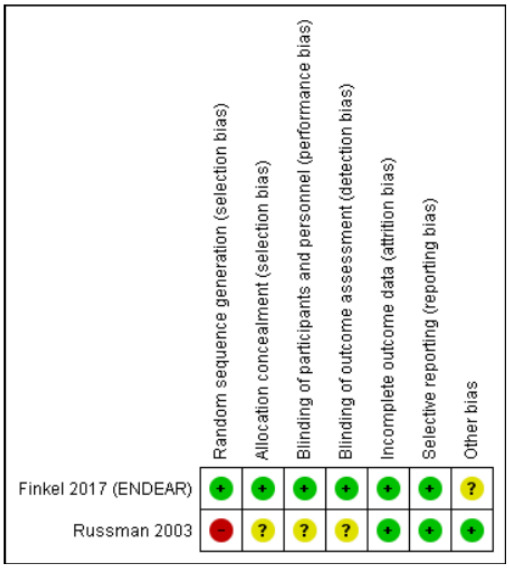
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 2 RCTs: one trial of intrathecal nusinersen in comparison to a sham (control) procedure in 121 randomised infants with SMA type I (Finkel 2017 [ENDEAR]), which was newly included at this update, and one small trial comparing riluzole treatment to placebo in 10 children with SMA type I (Russman 2003).

Qualität der Studien:



Ergebnisse:

Summary of findings for the main comparison. Intrathecal injected nusinersen compared to sham procedure for infants with SMA and 2 *SMN2* copies

Intrathecal injected nusinersen compared to sham procedure for infants with SMA and 2 *SMN2* copies

Patient or population: infants with SMA and 2 *SMN2* copies
Setting: in-hospital treatment for outpatient clinic
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				
Time from birth until death or full-time ventilation[a] Follow-up: range 6 months to 13 months[c]	Study population 68 per 100	**46 per 100** (31 to 64)	**HR 0.53** (0.32 to 0.89)	121 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	This represents a 47% lower risk of death or full-time ventilation with nusinersen than with the sham procedure
Acquisition of head control within one year after the onset of treatment Follow-up: range 6 months to 13 months[c]	0 of 37 participants	16 of 73 participants in the nusinersen-treated group achieved head control	**RR 16.95** (1.04 to 274.84)	110 (1 RCT)	⊕⊕⊖⊖ Moderate[d]	
Acquisition of the ability to sit within one year after the onset of treatment Follow-up: range 6 months to 13 months[c]	0 of 37 participants	6 of 73 participants in the nusinersen-treated group achieved the ability to sit independently	**RR 6.68** (0.39 to 115.38)	110 (1 RCT)	⊕⊕⊖⊖ Moderate[d]	
Acquisition of the ability to stand within one year after the onset of treatment Follow-up: range 6 months to 13 months[c]	0 of 37 participants in the sham procedure group	1 of 73 participants in the nusinersen-treated group achieved the ability to stand	**RR 1.54** (0.06 to 36.92)	110 (1 RCT)	⊕⊕⊖⊖ Moderate[d]	
Change in motor disability score - response on HINE-2 within one year after the onset of treatment[e] Follow-up: range 6 months to 13 months	0 of 37 participants in the sham procedure group	37 of 73 participants in the nusinersen-treated group showed a motor milestone response on the HINE-2	**RR 38.51** (2.43 to 610.14)	110 (1 RCT)	⊕⊕⊖⊖ Moderate[d]	
Adverse events attributable to treatment Measured as adverse events (all) Follow-up: range 6 months to 13 months	**Study population** 976 per 1000	**966 per 1000** (898 to 1000)	**RR 0.99** (0.92 to 1.05)	121 (1 RCT)	⊕⊕⊕⊖ Moderate[f]	Including bleeding risk from thrombocytopenia, renal toxicity, hyponatraemia, reduced growth, rash and possible (cerebral) vasculitis, hepatotoxicity, QTc interval prolongation on electrocardiogram, aspiration, infections, gastrointestinal problems
Severe adverse events attributable to treatment Measured as severe adverse events (all) Follow-up: range 6 months to 13 months	Study population 805 per 1000	**563 per 1000** (443 to 716)	**RR 0.70** (0.55 to 0.89)	121 (1 RCT)	⊕⊕⊕⊖ Moderate[f]	Including respiratory problems, cardiorespiratory arrest, death, brain injury, hypoxic ischaemic encephalopathy

***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).

CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; **HINE-2**: Hammersmith Infant Neurological Examination-Section 2; **CI**: confidence interval; **HR**: hazard ratio; **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]Defined as a requirement for 16 hours of ventilation per day regardless of whether via tracheostomy, tube or mask.
[b]We downgraded the certainty of the evidence once for risk of bias and imprecision (not sufficient to downgrade once for each). A slight baseline imbalance meant that children in the nusinersen-treated group had an earlier onset and were more severely affected by respiratory and bulbar problems. This baseline imbalance in factors related to respiratory decline would tend to favour the control intervention for this outcome. Although the effect of nusinersen is large, there is some degree of uncertainty in the effect estimate arising from imprecision in a single study of this size.
[c]Based on the final analysis. An interim analysis of motor milestones (HINE-2) was performed on all participants who had a day 183 visit. The study was then stopped for significant benefit from nusinersen. Final analysis was performed on data including participants fulfilling at least six months of trial enrolment.
[d]We downgraded the certainty of the evidence once for risk of bias and imprecision (not sufficient to downgrade once for each). There was slight baseline imbalance and there is some degree of uncertainty in the effect estimate arising from imprecision in a single study of this size. We did not downgrade the motor milestone outcome results further for imprecision, in spite of wide CI. The absence of events in the control group is consistent with the natural history of SMA type 1 and a response represents a large treatment effect.
[e]Response was defined according to scores on the HINE-2, which assesses the development of motor function through the achievement of motor milestones; in this trial, the scores accounted for 7 of the 8 motor milestone categories, excluding voluntary grasp. Infants were considered to have a motor milestone response if they met the following two criteria: improvement in at least one category (i.e. an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point, an increase in the score for kicking of ≥ 2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening (i.e. a decrease was defined as ≥ 1 point decrease in the score for head control, rolling, sitting, crawling, standing, or walking and a decrease in the score for kicking was defined as a decrease of ≥ 2 points).
[f]We downgraded one level for imprecision because the small sample size and shortened study duration mean that the study is unlikely to have captured uncommon adverse events.

- The RCT of intrathecally-injected nusinersen was stopped early for efficacy (based on a predefined Hammersmith Infant Neurological Examination-Section 2 (HINE-2) response). At the interim analyses after 183 days of treatment, 41% (21/51) of nusinersen-treated

infants showed a predefined improvement on HINE-2, compared to 0% (0/27) of participants in the control group. This trial was largely at low risk of bias.

- Final analyses (ranging from 6 months to 13 months of treatment), showed that fewer participants died or required full-time ventilation (defined as more than 16 hours daily for 21 days or more) in the nusinersen-treated group than the control group (hazard ratio (HR) 0.53, 95% confidence interval (CI) 0.32 to 0.89; N = 121; a 47% lower risk; moderate-certainty evidence). A proportion of infants in the nusinersen group and none of 37 infants in the control group achieved motor milestones: 37/73 nusinersen-treated infants (51%) achieved a motor milestone response on HINE-2 (risk ratio (RR) 38.51, 95% CI 2.43 to 610.14; N = 110; moderate-certainty evidence); 16/73 achieved head control (RR 16.95, 95% CI 1.04 to 274.84; moderate-certainty evidence); 6/73 achieved independent sitting (RR 6.68, 95% CI 0.39 to 115.38; moderate-certainty evidence); 7/73 achieved rolling over (RR 7.70, 95% CI 0.45 to 131.29); and 1/73 achieved standing (RR 1.54, 95% CI 0.06 to 36.92; moderate-certainty evidence). Seventy-one per cent of nusinersen-treated infants versus 3% of infants in the control group were responders on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) measure of motor disability (RR 26.36, 95% CI 3.79 to 183.18; N = 110; moderate-certainty evidence).
- Adverse events and serious adverse events occurred in the majority of infants but were no more frequent in the nusinersen-treated group than the control group (RR 0.99, 95% CI 0.92 to 1.05 and RR 0.70, 95% CI 0.55 to 0.89, respectively; N = 121; moderate-certainty evidence).
- In the riluzole trial, three of seven children treated with riluzole were still alive at the ages of 30, 48, and 64 months, whereas all three children in the placebo group died. None of the children in the riluzole or placebo group developed the ability to sit, which was the only milestone reported. There were no adverse effects. The certainty of the evidence for all measured outcomes from this study was very low, because the study was too small to detect or rule out an effect, and had serious limitations, including baseline differences. This trial was stopped prematurely because the pharmaceutical company withdrew funding.

Anmerkung/Fazit der Autoren

Based on the very limited evidence currently available regarding drug treatments for SMA type 1, intrathecal nusinersen probably prolongs ventilation-free and overall survival in infants with SMA type I. It is also probable that a greater proportion of infants treated with nusinersen than with a sham procedure achieve motor milestones and can be classed as responders to treatment on clinical assessments (HINE-2 and CHOP INTEND). The proportion of children experiencing adverse events and serious adverse events on nusinersen is no higher with nusinersen treatment than with a sham procedure, based on evidence of moderate certainty. It is uncertain whether riluzole has any effect in patients with SMA type I, based on the limited available evidence. Future trials could provide more high-certainty, longer-term evidence to confirm this result, or focus on comparing new treatments to nusinersen or evaluate them as an add-on therapy to nusinersen.

3.3 Systematische Reviews

Meylemans A et al., 2019 [4].

Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review

Fragestellung

We wanted to verify the current evidence of efficacy concerning improvements in motor function, achieving motor milestones (MM) and survival of intrathecal administration of nusinersen in SMA patients versus standard medical care.

Methodik

Population:

- SMA patients

Intervention:

- Intrathecal nusinersen

Komparator:

- standard medical care

Endpunkte:

- improvements in motor function, achieving MM, survival

Recherche/Suchzeitraum:

- MEDLINE and CENTRAL search on December 21 2018, respectively, via PubMed
- In order to update our search, a second search was performed on April 22, 2019

Qualitätsbewertung der Studien:

- The quality of the studies was appraised according to the classification levels of evidence using the Evidence-Based Guideline Development (EBRO) classification of the Dutch Cochrane Centre. Level of evidence was also considered based on the EBRO and Oxford 2009 level of evidence criteria and the American Academy of Neurology (AAN) classification of evidence matrix. Grade of recommendation was based on the Oxford 2009 criteria, and quality was interpreted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) discriminatory instrument.

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, four studies remained, of which two had more than 120 subjects, both two phase-3 randomized controlled trials (RCTs) and two studies of 20–28 subjects, a phase-2 open-label clinical trial and a phase-1 open-label clinical trial.

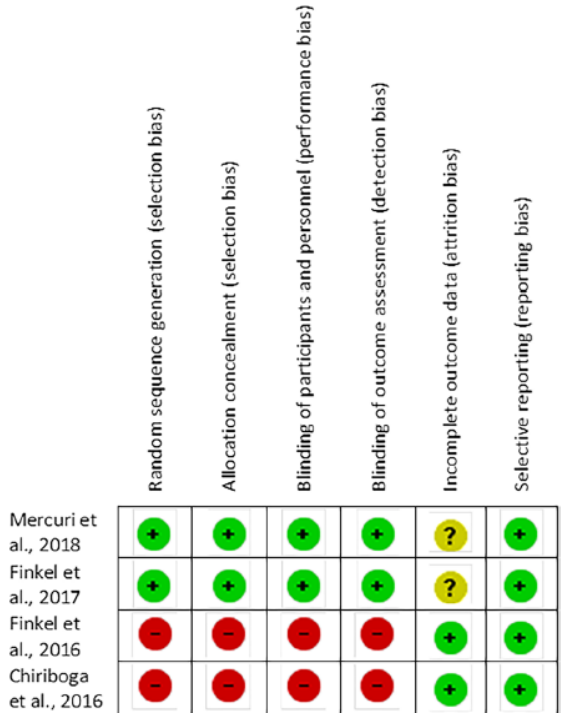
Charakteristika der Studien und Population:

- CHERISH TRIAL — is a multicenter randomized, double- blind, sham-procedure-controlled phase-3 study that tested the clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen over 15 months in patients with later-onset SMA. Only patients with documented SMN1 mutations with onset of symptoms above the age of 6 months old, age

2–12 years old at screening, who could sit independently but had never reached the ability to walk independently and Hammersmith Functional Motor Scale-Expanded (HFMSE) ranging 10–54, were included. Patients were randomized in a 2:1 ratio to receive a dose of 12 mg intrathecal nusinersen or a sham-procedure four times over 15 months. A total of 126 patients were randomized, 84 in the intervention group, 42 in the control group.

- ENDEAR TRIAL — is a multicenter randomized, double-blind, sham-procedure-controlled phase-3 study that tested clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen over 13 months in patients with infantile-onset SMA. Only patients with genetic documentation of SMA and SMN2 copy number of 2 with onset of symptoms after 1 week, but before 6 months and age less than 7 months at screening were included. Patients were randomized in a 2:1 ratio to receive an equivalent dose (EqD) of 12 mg intrathecal nusinersen or a sham-procedure six times. A total of 121 patients were randomized, 80 in the intervention group, 41 in the control group.
- Finkel et al. TRIAL — is a multicenter open-label, dose-escalation phase-2 trial that tested the clinical efficacy of multiple doses of nusinersen (6 mg and 12 mg dose equivalents), safety, tolerability and pharmacokinetics of intrathecal nusinersen in patients with infantile-onset SMA. Only patients with genetic documentation of SMA with onset of symptoms between 3 weeks and 6 months were included. Twenty patients were selected.
- Chiriboga et al. (2016) TRIAL — is a multicenter open-label ascending single-dose phase-1 trial that tested the preliminary clinical efficacy, safety, tolerability and pharmacokinetics of intrathecal nusinersen in patients with later-onset SMA. Data included in the report are baseline evaluations for a follow-up study. Only patients with genetic documentation of SMA with age at screening between 2 and 14 years old were included. Twenty-eight patients were selected. Nusinersen 1 mg, 3 mg and 6 mg was administrated to six patients each time, and ten patients received nusinersen 9 mg.

Qualität der Studien:



Ergebnisse:

Motor function and motor milestones

- CHERISH
  - significant between-group difference favoring nusinersen (least-squares mean difference in change 5.9 points; 95% confidence interval (CI) 3.7–8.1; P < 0.001).
  - significant difference in the proportion of subjects who achieved a 3-point or greater increase from baseline in HFMSE. More than half of the patients in the treatment group had a clinically meaningful increase in HFMSE score of at least three points with greatest improvements in younger children and those who received treatment early.
  - There was a non-significant difference in the achievement of new World Health Organization (WHO) MM (II, moderate).
- ENDEAR
  - significantly higher percentage of infants in the nusinersen group had a MM response (41% vs. 0%, P < 0.001) (I, high)
  - one secondary endpoint significantly favoured nusinersen, namely response on Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOPINTEND) score (71% vs. 3%, P < 0.001) (I, moderate).
- Finkel et al.
  - significant change in HINE-2 score for both cohorts combined and in the 12 mg group was described, P = 0.0002 and P < 0.0001, respectively (III, very low).
  - CHOP-INTEND score showed a mean increase of 11.5 points (III, very low).
- Chiriboga et al.
  - significant improvement in HFMSE in the 9 mg group at 85 days and at 9–14 months was noticed with mean increase in HFMSE + 3.1 points or + 17.6% (P = 0.016) and + 5.8 points or + 32.8% (P = 0.008) (IV, very low).

Survival

- ENDEAR
  - 'event-free survival' was significantly better for the intervention group [61% vs. 32%; Hazard Ratio 0.53 (95% CI) 0.32–0.89; P = 0.005] (I, moderate). This was most pronounced among infants with a disease duration at screening no longer than the median duration of 13.1 weeks, and a significantly lower percentage of infants in the treatment group had died.
  - The secondary endpoint 'survival' was also significantly favoring nusinersen [84% vs. 61%; Hazard ratio 0.37 (95% CI) 0.18–0.77; P = 0.004] (I, moderate).
  - The secondary endpoint 'permanent ventilation' was not significantly different among patients treated with nusinersen and the control group (I, moderate).

Safety

- None of the RCTs reported new safety concerns. The were similar in the treatment and control group. The majority of AEs were deemed unlikely or not related to study treatment and could be explained by another cause such as SMA or concomitant therapy for another disorder.

Anmerkung/Fazit der Autoren

Because of heterogeneity in design, population and outcome measures, no meta-analysis could be performed.

Although several statements are level I recommendations, we think these findings should be scrutinized. Both RCTs were terminated early because the primary endpoint at the pre-specified interim analysis was reached and found statistically significant. A multiple-imputation method to account for missing data was used and included 54 (35:19) patients in the CHERISH trial. In the CHERISH trial, a sample size of 117 patients was estimated to give the trial at least 90% power to detect a mean difference of three points in HFMSE score. In the final analysis, complete observational data were available for 100 patients. The data imputation method was used to include 126 patients in total. Because of the lack of observational data, the real effect size of treatment is unclear.

Based on statistical considerations, significance of the primary endpoints was not evaluated in the final analysis in both trials, and using a hierarchical strategy no significance analyses were performed on all secondary endpoints. Because of strict inclusion criteria, the investigated population might be younger and more homogenous and therefore not representative for the overall group of SMA patients. Limitations of the non-RCTs are, besides the study design, the small number of included patients and relatively short duration of follow-up.

There is level I evidence for recommendation of intrathecal nusinersen 12 mg or 12 mg EqD in patients with early- and later-onset SMA to obtain improvement in motor function and to develop MM. There is also level I evidence that this treatment prolongs event-free survival and survival in patients with SMA type 1. We suggest that nusinersen should be administered in patients with early- and later onset SMA as early as diagnosis is sure. Currently, there is insufficient evidence of efficacy in SMA types 3 and 4, or start of treatment in adults. The clinical spectrum of patients with SMA is also broader than that of the included patients in the studies. Therefore, there is need for studies with broader inclusion criteria to cover the more heterogeneous population, also including more different SMA types and age categories, including adults.

Treatment with intrathecal nusinersen in patients with early- and later-onset SMA results in significant and clinically meaningful improvement in motor function (I, high in SMA type 1, moderate in later-onset SMA)—but does not restore age-appropriate function—with better improvement if started earlier in disease course and results in prolonged event-free survival and survival in patients with SMA type 1 (I, moderate). Intrathecal nusinersen has an acceptable safety and tolerability profile. Further trials regarding long-term effects and safety aspects as well as trials including broader SMA and age categories are required and ongoing.

3.4 Leitlinien

Mercuri E et al., 2018 [3].

Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

Siehe auch: **Finkel RS et al., 2018 [1].**

Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

Fragestellung

Here we report a two-part update of the topics covered in the previous recommendations. In part 1 we present the methods used to achieve these recommendations, and an update on diagnosis, rehabilitation, orthopedic and spinal management; and nutritional, swallowing and gastrointestinal management. Pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA are discussed in part 2.

Methodik

Grundlage der Leitlinie

- Die Mitglieder der Arbeitsgruppen sind benannt, der professionelle Hintergrund ist jedoch nicht für jedes Mitglied angegeben. An jeder Gruppe sollte eine betroffene Person bzw. ein Elternteil beteiligt sein. Eine betroffene Person nahm am internationalen Workshop teil.
- Interessenkonflikte und finanzielle Unabhängigkeit sind nicht dargelegt. Die Ergebnisse der Arbeitsgruppen wurden den pharmazeutischen Unternehmen zum Review und zur Kommentierung vorgelegt, die derzeit an Arzneimitteln für die Erkrankung arbeiten. Es ist nicht beschrieben, wie mit diesen Kommentaren umgegangen wurde.
- Keine Angaben bezüglich einer systematischen Suche, Auswahl und Bewertung der Evidenz. Es wurden für die Fragestellungen der einzelnen Arbeitsgruppen Literaturrecherchen vorgenommen, es sind aber keine Recherchestrategien dargelegt und es ist unklar, ob die Recherche systematisch erfolgte. Für die Empfehlungen liegen Evidenztabellen vor, in denen die Qualität der Evidenz von A bis D bewertet wird.
- Es wurden Delphi-Gruppen durchgeführt. Wie die Konsensusprozesse genau durchgeführt wurden ist nicht angegeben. Es wurde ein externes Begutachtungsverfahren durch pharmazeutische Unternehmen durchgeführt, ob weitere Reviews durchgeführt wurden ist unklar.
- Empfehlungen werden im Text gegeben. Einige Empfehlungen werden mit Empfehlungsstärken angegeben. Es gibt unterschiedliche Empfehlungsstärken, es ist aber nicht dokumentiert, wie diese zustande kamen. Die zugrundeliegende Evidenz ist zum Teil aber nicht immer im Text dargestellt.
- Keine Angaben über Aktualisierungen.

Recherche/Suchzeitraum:

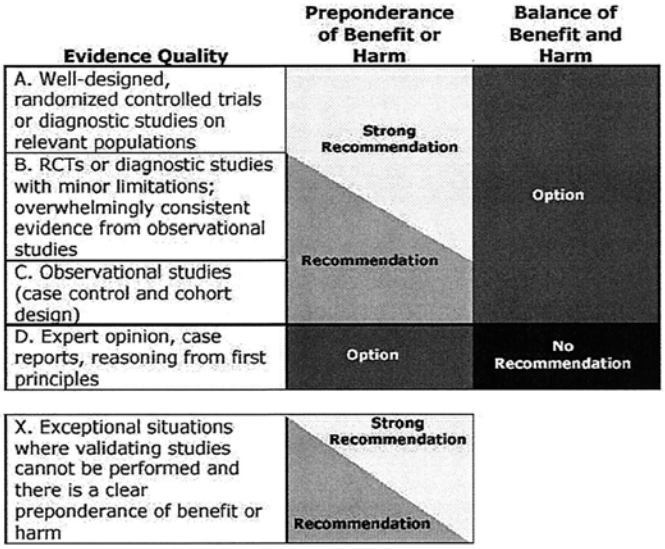
- Keine Angabe

GoR

- In den Evidenztabellen ist der Empfehlungsgrad angegeben mit strong, moderate, divided oder lack of consensus, es ist aber nicht dargelegt, wie die Bewertungen definiert sind und wie sie zustande kamen.

LoE

- Für einige Empfehlungen liegen Evidenztabellen vor, in denen die Qualität der Evidenz von A bis D bewertet wird.



Sonstige methodische Hinweise

- Die Leitlinie entspricht keiner S3 Leitlinie und wurde aus Mangel an höherwertiger Evidenz aufgenommen.
- Patient*innen werden je nach funktionalem Status in nonsitter, sitter und walker unterteilt.
- Update einer Konsensus-Leitlinie von 2007.

Empfehlungen

Orthopedic care: assessment and intervention

Topic	Aggregate Evidence Quality	Expert Opinion Consensus	Degree of impact	Recommendation
Orthotic management of scoliosis skeletally immature patients	D	Divided	High	Orthotic management may be considered for major curve with Cobb angle 15-30˚ Majority of respondents recommend orthotic management for moderate spinal deformity where major curve Cobb angle >30-50˚
Growth-friendly instrumentation for scoliosis treatment skeletally immature patients (< 10years)	D	Strong	High	Growth-friendly, non-fusion, posterior spine instrumentation should be implemented in skeletally immature patients (<10yrs) with severe spinal deformity major curve Cobb angle ≥ 50˚
Posterior spinal fusion for treating scoliosis in	D	Strong	High	Multi-segmental, posterior spinal instrumentation with fusion should be implemented in skeletally

skeletally mature patients				mature patients (closed tri-radiate cartilage) with major curve Cobb angle ≥ 50˚
Importance of patient age as determinant for type of spinal instrumentation	D	Strong	High	Patients with large, progressive curves should be treated surgically, with type of spine instrumentation based on patient age
Age for growth-friendly instrumentation for scoliosis	D	Strong	High	Patients 4 to 8 years of age with large, progressive curves should be instrumented with growth-friendly instrumentation
Age for multi-segmental posterior spinal instrumentation and fusion	D	Strong	High	Patients >12 years of age with large, progressive curves should be instrumented with multi-segmental fixation and undergo definitive spinal fusion
Use of Magnetically controlled growing rods (MCGRs) as an alternative to traditional growing rods for treating skeletally immature patients with scoliosis	D	Strong	High	The advantage of MCGRs is the decrease in repetitive surgeries; therefore MCGRs should be used as an alternative to traditional growing rods.
Should growth-friendly instrumentation be converted to definitive spinal fusion once a patient has reached skeletal maturity?	D	Strong	High	Growth-friendly instrumentation should be converted to definitive spinal fusion on a case-by-case basis.

Pulmonary care recommendations

Non-sitters

Nebulized bronchodilators should be available if there is suspicion for asthma. Nebulized mucolytics, 3% or 7% hypertonic saline or dornase-α (Pulmozyme®) should not be used long-term as there is no evidence to support its use. Furthermore, if 3% or 7% saline is used beyond the therapeutic need it can thin secretions of normal viscosity thereby increasing secretion burden. Glycopyrrolate should be used with caution to treat hypersalivation with great care to adjust the dose to attain the proper effect, and avoid over drying of secretions, which may contribute to the development of mucus plugs. There was no consensus for the injection of botulinum toxin into the salivary glands or other methods to reduce production of oral secretions. Palivizumab should be given during RSV season as determined by regional RSV activity through the first 24 months of life, and influenza vaccination should be administered annually after 6 months of age. Gastroesophageal reflux should be searched for and treated when present.

Sitters

Nebulized bronchodilators should be available if there is high suspicion for asthma or a clear clinical improvement after administration. Nebulized mucolytics should not be used long term. Annual influenza and pneumococcal immunizations should be administered per standard pediatric recommendations for patients with chronic neuromuscular conditions.

Medication, supplements and immunizations

Until recently no drug treatment had proved to be able to influence the disease course of SMA. A Cochrane review published in 2012 reported six randomized placebo-controlled trials on treatment for SMA using creatine, phenylbutyrate, gabapentin, thyrotropin-releasing hormone, hydroxyurea and combination therapy with valproate and acetyl-L-carnitine [36,37]. None of these studies showed statistically significant effects on the outcome measures in participants with SMA types 2 and 3. Others have reported using other possible therapeutic approaches, such as albuterol, a beta-adrenergic agonist that showed promising functional improvements in open label studies [38,39].

Despite the lack of evidence from randomized placebo-controlled trials, some of these drugs, especially albuterol, are often used in some countries in clinical practice in sitters and ambulant patients. Antibiotics or medications/supplements for bone health, such as vitamin D and calcium and bisphosphonate, or drugs for gastroesophageal reflux, were recommended with the exception of vitamin D, rarely used prophylactically, and mainly used if needed/deficient. These are discussed in the sections dedicated to bone health and nutrition. Annual influenza and pneumococcal immunizations, as reported in the pulmonary section, were strongly recommended.

At the time the consensus process was completed, none of the drugs involved in clinical trial had completed the regulatory process and were commercially available. Nusinersen (Spinraza™), an antisense oligonucleotide that had completed phase 3 clinical trials in both type 1 and type 2 SMA [3,40,41], received recent approval both by the United States Food and Drug Administration and by the Agency for Medicines Agency in Europe for the treatment of all SMA types and has become commercially available in several countries. While the early patient and family clinical outcomes have been very favorable, because nusinersen is intrathecally administered, there is a required institutional infrastructure to provide administration and post-procedural monitoring in a reliable way. In addition the cost of the medication has made long term insurance company approval uncertain.

Olesoxime, a neuroprotective drug, has completed a phase 3 trial in patients with type 2 and 3 SMA, but the primary endpoint was not met. Secondary endpoints and sensitivity analyses indicate that olesoxime might maintain motor function in patients with SMA [42]. Other approaches, such as small molecules aiming to increase SMN protein level or SMN1 gene replacement using viral vector, are also being used in clinical trials with promising preliminary results [43] and in the next few years the scenario is likely to rapidly change.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2021) am 11.03.2021

#	Suchfrage
1	[mh "spinal muscular atrophy"]
2	[mh ^"motor neuron disease"]
3	(motor NEXT neuron* NEXT disease*):ti,ab,kw
4	(spinal OR "bulbo spinal" OR bulbospinal OR myelopath* OR progressiv* OR spinobulbar):ti,ab,kw AND (muscular OR muscle):ti,ab,kw AND (atroph*):ti,ab,kw
5	(spinal OR (neurogenic NEXT scapuloperonea*)):ti,ab,kw AND (amyotroph*):ti,ab,kw
6	(spinal OR "bulbo spinal" OR bulbospinal OR spinobulbar OR spinopontin* OR "hereditary motor"):ti,ab,kw AND (neuronopath*):ti,ab,kw
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	#7 with Cochrane Library publication date from Mar 2016 to Mar 2021

Systematic Reviews in Medline (PubMed) am 11.03.2021

#	Suchfrage
1	"muscular atrophy, spinal"[mh]
2	(spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR myelopath*[tiab] OR progressiv*[tiab] OR spinobulbar[tiab]) AND (muscular[tiab] OR muscle[tiab]) AND atroph*[tiab]
3	(spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab]
4	(spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR

	scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2016/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 11.03.2021

#	**Suchfrage**
1	"muscular atrophy, spinal"[mh] OR "motor neuron disease"[mh:noexp]
2	motor[tiab] AND neuron*[tiab] AND disease*[tiab]
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4	(spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab]
5	(spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
8	(((#7) AND ("2016/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

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