Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-214 Omaveloxolon

Stand: Oktober 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Omaveloxolon **Friedreich-Ataxie** **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.	Stimm-, Sprech- und Sprachtherapie, Krankengymnastik nach Heilmittel-Richtlinie.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
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:	
Omaveloxolon ATC-Code Handelsname®	<u>Anwendungsgebiet laut Beratungsanforderung:</u> Patienten ≥16 Jahre mit Friedreich-Ataxie
Für das Anwendungsgebiet „Friedreich-Ataxie“ sind keine Arzneimittel zugelassen.	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-214 (Omaveloxolon)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. September 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AF	atrial fibrillation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BBS	Berg Balance Scale
FA/FRDA	Friedreich-Ataxie
FIM	Functional Independence Measure
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICARS	International Cooperative Ataxia Rating Scale
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LVEF	linksventrikuläre Ejektionsfraktion
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SARA	Scale for the Assessment and Rating of Ataxia
SIGN	Scottish Intercollegiate Guidelines Network
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Patienten ≥16 Jahre mit Friedreich-Ataxie.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Friedreich-Ataxie* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 26.08.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 292 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

keine

3.2 Systematische Reviews

Winser S et al., 2022 [5].

Effects of therapeutic exercise on disease severity, balance, and functional Independence among individuals with cerebellar ataxia: A systematic review with meta-analysis

Fragestellung

"this systematic review aims to examine the available evidence exploring the efficacy of therapeutic exercises on the disease severity, as assessed using the Scale for the Assessment and Rating of Ataxia (SARA) or the International Cooperative Ataxia Rating Scale (ICARS); balance, as assessed using the Berg Balance Scale (BBS) or the balance subscales of the SARA and ICARS; and functional independence, as assessed using the Functional Independence Measure (FIM) among adults with cerebellar ataxia"

Methodik

Population:

- Erwachsene Patienten mit degenerativer erblicher und nicht erblicher zerebellärer Ataxie oder Ataxie anderer Ursache sowie Kombinationen

Intervention:

- Physiotherapie

Komparator:

- Nicht definiert (keine Einschränkung auf vergleichende Studien)

Endpunkte:

- Krankheitsschwere (Scale for the Assessment and Rating of Ataxia – SARA bzw. International Cooperative Ataxia Rating Scale - ICARS), Gleichgewicht (Berg Balance Scale - BBS), funktionelle Unabhängigkeit (Functional Independence Measure - FIM)

Recherche/Suchzeitraum:

- Recherche in AMED, EBSCO, Embase, MEDLINE, CINAHL, Web of Science im Juli 2021, nur englischsprachige Artikel

Qualitätsbewertung der Studien:

- RCTs: Physiotherapy Evidence Database (PEDro) Scale
- Non-RCTs: Newcastle-Ottawa Scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 26, davon 8 RCTs, 2 Studien (davon 1 RCT) zu Friedreich-Ataxie, N=48

Charakteristika der Population:

- Durchschnittsalter in den 2 Studien zur FA: 35-36 J., keine weiteren Informationen

Qualität der Studien:

- RCT (PEDro): 7 von 10 Punkten
- unkontrollierte Studie (NOS): 7 von 9 Punkten

Studienergebnisse:

- 2 Studien (N=48) zur FA:
  - Verbesserungen im FIM nur in der Studie ohne Kontrollgruppe, kein Unterschied in RCTs: WMD 1,6 (95%-CI −1,5;4,6), I^2=0%, p=0,3, N=59; Qualität der Evidenz (GRADE): moderate

Anmerkung/Fazit der Autoren

„This review found low to moderate evidence from studies of low to high methodological quality that supports therapeutic exercises to reduce the disease severity among adults with non-hereditary degenerative cerebellar ataxia and improve balance among adults with acquired cerebellar ataxia."

Kommentare zum Review

Studienpopulationen sehr heterogen, daher wurden nur die Ergebnisse der Studien zur Friedreich-Ataxie dargestellt.

Zesiewicz TA et al., 2018 [6].

Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Fragestellung

"1. For patients with cerebellar motor dysfunction, do pharmacologic therapies, compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?

2. For patients with cerebellar motor dysfunction, do surgical or other interventional therapies (e.g., physical training), compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?

3. For patients with cerebellar motor dysfunction, does transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?"

Methodik

Population:

- Patienten mit zerebellären motorischen Funktionsstörungen

Intervention:

- Arzneimittel
- Nicht-medikamentöse Interventionen (inkl. Chirurgie und nicht-ärztliche Leistungen)
- Transkranielle Magnetstimulation oder transkranielle Gleichstromstimulation

Komparator:

- Keine Behandlung oder Alternativbehandlung

Endpunkte:

- Motorische Symptome, Sicherheit

Recherche/Suchzeitraum:

- Recherche in Medline und Embase, letztes Update Sept. 2016, Studien ohne Kontrollgruppe ausgeschlossen

Qualitätsbewertung der Studien:

- Gemäß Methodik der American Academy of Neurology (https://www.aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/17guidelineprocman_pg.pdf)

Ergebnisse

Anzahl eingeschlossener Studien:

- 32, davon 2 RCTs zu Riluzol bei Pat. u.a. mit FA

Charakteristika der Population:

- Studien schlossen Patienten mit Ataxien unterschiedlicher Genese ein

Qualität der Studien:

- s.u.

Studienergebnisse:

- Riluzol zur Reduktion der Ataxie:
  - SARA-Score nach 12 Monaten (50mg 2xtgl.) vs. Placebo: -2,68 (95%-CI -3,98;-1,39) (basiert auf 1 RCT[1] mit 55 Pat., davon 17 mit FA)
    - Qualität der Evidenz: moderat

Anmerkung/Fazit der Autoren

"In patients with SCA or FA, riluzole 100 mg/d is probably effective for improving ataxia as measured by the SARA at 12 months (1 Class I study)."

Kommentare zum Review

Unklar ob Ergebnisse zur Reduktion der Ataxie zwischen Indikationen übertragbar sind

[1] Romano S, Coarelli G, Marcotulli C, et al. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2015;14:985-91.

3.3 Leitlinien

keine

3.4 Sonstige Quellen ohne systematische Evidenzbasierung

Groh WJ et al., 2022 [4].

2022 HRS expert consensus statement on evaluation and management of arrhythmic risk in neuromuscular disorders

Heart Rhythm Society (HRS), in collaboration with the American Academy of Physical Medicine and Rehabilitation (AAPM&R), the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Anesthesiologists (ASA), the Asia Pacific Heart Rhythm Society (APHRS), the Child Neurology Society (CNS), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the Pediatric and Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC)

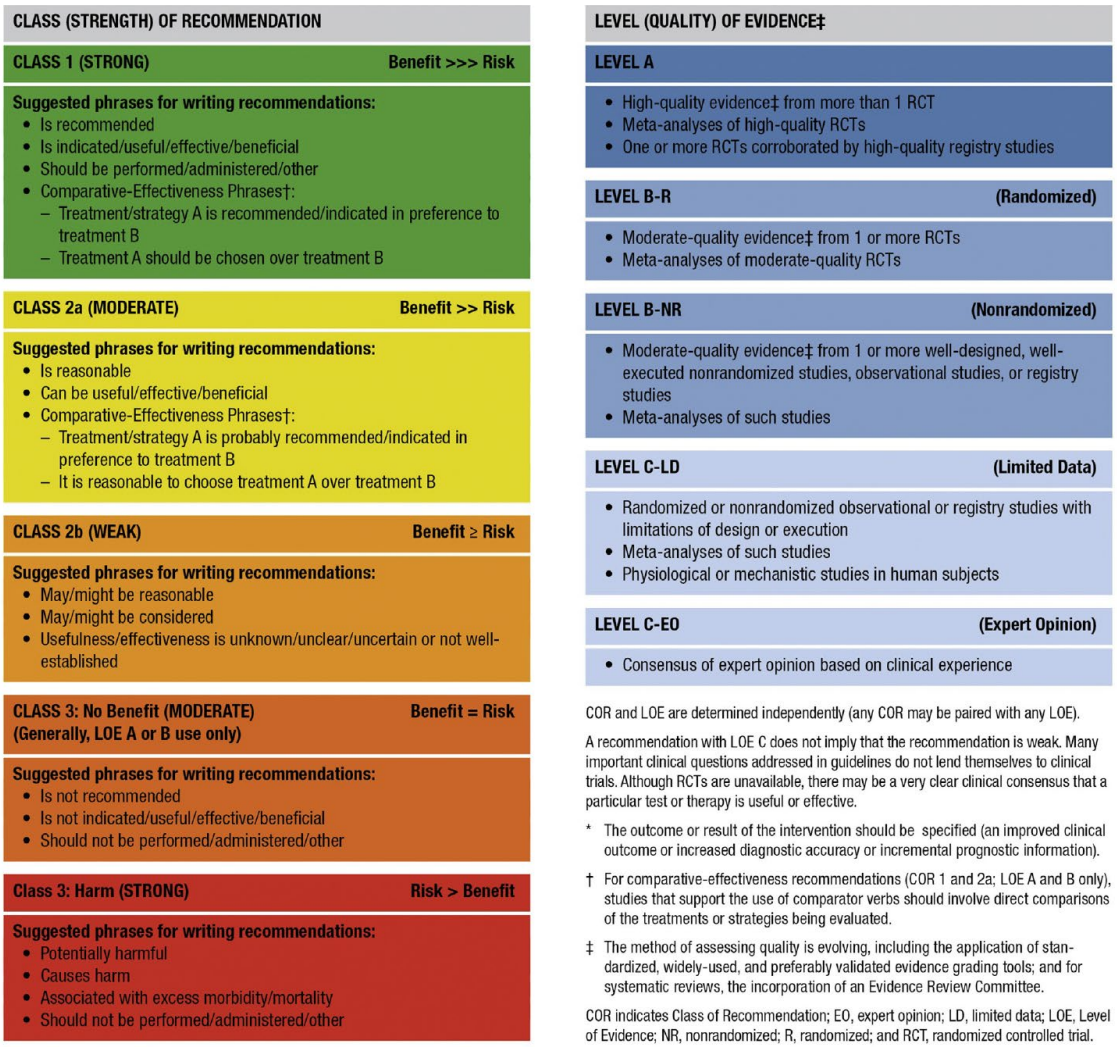
Methodik:

"This consensus document provides recommendations for care of these complex patients based on current evidence for best practice in the assessment and management of arrhythmia risk in patients with NMDs. When evidence was lacking or contradictory, a consensus expert opinion was developed."

"Disclosure of any relationships with industry and other entities (RWIs) was required from the writing committee members and from the peer reviewers" (https://www.sciencedirect.com/science/article/pii/S1547527122019464?via%3Dihub#appsec1)

"The HRS Scientific and Clinical Documents Committee establishes, reviews, and updates clinical practice document methodology, with the aim to align with Institute of Medicine standards."

"The recommendations were formulated according to the ACC/AHA class of recommendation (COR) and level of evidence (LOE) system"



CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Hinweis:

Recherche beschrieben, aber kein Recherchedatum

Empfehlungen:

7.3 Bradykardien

- In patients with mitochondrial myopathies including FA and documented symptomatic bradycardia due to sinus node dysfunction or any degree of AV block, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:1
- In patients with mitochondrial myopathies including FA and third-degree or advanced second-degree AV block at any anatomical level, with or without symptoms, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:1
- In patients with FA with an LVEF ≤35% despite guideline-directed medical therapy, with a combination of sinus rhythm, LBBB, QRS duration ≥150 ms, and NYHA class II to class IV symptoms, or in those with suspected right ventricular pacing–induced

cardiomyopathy or anticipated right ventricular pacing ≥40%, CRT is reasonable if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:2a
- In patients with mitochondrial myopathies including FA with progressive ECG conduction disorder including any degree of AV or fascicular block, permanent pacemaker implantation is reasonable if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:2a

7.4 Vorhof-Arrhythmien

- In patients with mitochondrial myopathies including FA, anticoagulation according to established guidelines and clinical context is recommended for AF or AFL, taking into consideration the risks of thromboembolism and the risks of bleeding on oral anticoagulation.
  - LoE: B-NR, COR:1

7.5 ventrikuläre Arrhythmien

- In patients with mitochondrial myopathies including FA with spontaneously occurring VF or sustained hemodynamically significant VT, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:1
- In patients with mitochondrial myopathies including FA with an LVEF ≤35% despite guideline-directed medical therapy, ICD therapy is reasonable if concordant with the patient's goals of care and clinical status.
  - LoE: B-NR, COR:2a

Referenzen:

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Wahbi K, Bougouin W, Behin A, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. Eur Heart J 2015;36:2886–93.
Dhingra RC, Denes P, Wu D, Chuquimia R, Rosen KM. The significance of second degree atrioventricular block and bundle branch block: observations regarding site and type of block. Circulation 1974;49:638–46.
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De Silva R et al., 2019 [1,3].

European Reference Network for Rare Neurological Diseases (ERN-RND) and Ataxia UK

Management of the ataxias towards best clinical practice; 3rd edition. Including update: de Silva et al (2019), OJRD Guidelines on the diagnosis and management on the progressive ataxias; Version 2.0

Ziel:

"These guidelines focus on the progressive ataxias, and exclude disorders where ataxia is an epiphenomenon of another neurological condition. Specifically, the recommendations cover the inherited ataxias (e.g. FRDA, SCAs), idiopathic sporadic cerebellar ataxia and specific neurological conditions in which ataxia is the dominant symptom (e.g. MSA-C)."

Methodik:

Recherche in PubMed, MEDLINE, Cochrane Database of Systematic Reviews, EMBASE, Scopus, keine weiteren Informationen.

LoE: nach Hillier et al. FORM: an Australian method for formulating and grading recommendations in evidence-based clinical guidelines. BMC Med Res Methodol 2011;11:23.

GoR: nach National Health and Medical Research Council, A. G. In: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines; 2009.

Hinweis:

Die LL-Empfehlungen sind nicht spezifisch für FA, aber umfassen diese.

Empfehlungen:

Table 4 Symptomatic treatments

4.1 Spasticity

Recommendation	Grade
Careful assessment by a neurologist, with advice from a physiotherapist, is required to decide on the type of treatment of spasticity.	GPP
Consider physiotherapy first to treat spasticity, and if that does not provide complete benefit use pharmacological treatment. Surgery should be considered in cases where physiotherapy and pharmacological treatments have not worked.	GPP
For pharmacological treatment of generalised spasticity consider using the following oral medications (usually in this order due to the profile of side effects and better tolerability): baclofen, tizanidine, gabapentin, clonazepam, dantrolene sodium or diazepam.	GPP
To treat focal spasticity refer to a specialised clinic for treatment with intramuscular botulinum toxin injections, followed by physiotherapy.	GPP

4.2 Tremor

Recommendation	Grade
Patients with ataxia who have tremors should be offered pharmacological treatment using Propranolol, Primidone, Propranolol and Primidone in combination, Topiramate, Clonazepam and Gabapentin (in this order).	GPP
In patients where tremor is extremely debilitating and not responsive to medication a referral to a centre specialising in functional neurosurgery should be considered.	D [15–18]

4.3 Dystonia

Recommendation	Grade
Focal dystonia should be treated with botulinum toxin injections.	GPP
Generalised dystonia should be treated with oral medications, followed by surgery if this is not effective.	GPP
Patients with dystonic tremor should be offered physiotherapy and oral medications followed by surgery if the former are ineffective.	GPP

4.4 Scoliosis

Recommendation	Grade
Regular surveillance of the development of scoliosis in FRDA patients (especially children) is recommended as it is important for it to be treated.	GPP
If scoliosis is detected, referral to a physiotherapist and spinal surgeon is recommended.	GPP
For mild scoliosis the patient should be kept under close observation and the spinal surgeon should consider treatment with bracing.	B [19–21]
For severe scoliosis consider surgery to straighten the spine.	B [22, 23]
Regular follow-up by a spinal surgeon is recommended after an operation on the spine.	B [22, 23]

4.5 Pain

Recommendation	Grade
Treat pain with physiotherapy and/or pharmacological treatments.	GPP
Consider use of the following drugs to treat neuropathic pain: Amitriptyline, Nortriptyline, Carbamazipine, Pregabalin, Gabapentin and Duloxetine.	GPP

Table 4 Symptomatic treatments *(Continued)*

Consider referral to a pain management clinic if pain is severe or limiting daily activities.	GPP
4.6 Cardiac involvement in FRDA	
Recommendation	Grade
When FRDA is diagnosed a referral to a cardiologist is recommended for the early diagnosis of cardiac problems and the management of cardiac complications, where required.	GPP
Regular screening by a cardiologist is recommended in FRDA patients; once every two years before any cardiac disease is documented, and at least annually after manifesting features of asymptomatic cardiac disease.	GPP
Transthoracic Echocardiography and ECG should be used for the diagnosis and monitoring of the myocardial changes.	GPP
Holter monitoring should be undertaken to detect silent cardiac arrhythmias or the association of symptoms (such as palpitations, shortness of breath) with the underlying rhythm.	GPP
A cardiologist should consider pharmacological treatment (including the use of anticoagulants), and in some cases the implantation of pacing devices, in collaboration with the neurologist.	GPP
4.7 Bladder problems - lower urinary tract dysfunction	
Recommendation	Grade
In primary care, test for urinary tract infection and measure post-void residual (to exclude common causes of urgency and frequency). If these are normal, check for other common causes such as prostate enlargement.	GPP
Practical advice should be given about cutting down caffeine, fizzy drinks and alcohol, as well as information about timed voiding and bladder retraining whenever appropriate. The fluid intake should be individualized; a fluid intake of between 1 to 2 L a day is recommended (taking into consideration possible concurrent cardiac issues).	GPP
Advice on pelvic floor exercises should be given as it may be helpful especially when symptoms are mild.	GPP
Most individuals with overactive bladder symptoms will require antimuscarinic medications (such as tolterodine, oxybutynin, propiverine and solifenacin).	GPP
In patients with cardiac complications and/or cognitive problems caution is advised when using antimuscarinic medications.	GPP
In patients with cognitive problems, more selectively-acting antimuscarinic medications, such as trospium chloride or darifenacin should be considered.	GPP
In some instances, referral to an urologist is recommended eg: in cases of haematuria or suspicion of concomitant urological condition.	GPP
4.8 Gastroenterological problems	
Recommendation	Grade
Suggest changes in lifestyle (eg: diet, fluid and mobility assistance) for patients with constipation, followed by the use of laxatives or suppositories.	GPP
Consider referral for specialist assessment if patients have urgency and faecal incontinence.	GPP
4.9 Sexual dysfunction	
Recommendation	Grade

Table 4 Symptomatic treatments *(Continued)*

Consider discussing sexual function with male patients due to the potential for erectile dysfunction.	GPP
Treat erectile dysfunction where appropriate with phosphodiesterase-5 inhibitors. Treatment decisions should balance the needs of the person and the potential side effect of medications e.g., hypotension.	GPP
If patients have cardiac pathologies caution should be exercised when considering medication, and consultation with a cardiologist is recommended.	GPP
4.10 Swallowing and dysphagia	
Recommendation	Grade
If patients show symptoms of dysphagia a referral to a speech and language therapist should be made (see Additional file 1: Table S2).	GPP
If there is unintentional weight loss due to dysphagia consider the use of nutritional supplements and refer to a dietician.	GPP
If calorie intake cannot be maintained despite supplements, discuss the possibility of a percutaneous gastronomy (PEG) to provide secure feeding.	GPP
4.11 Sialorrhoea (excessive salivation)	
Recommendation	Grade
Sialorrhoea is normally associated with dysphagia, thus a referral to a speech and language therapist is recommended for assessment of swallow.	GPP
Treat sialorrhoea and thick secretions according to Bavikatte et al. 2012 [9] (and the full guidelines).	GPP
4.12 Audiology and hearing	
Recommendation	Grade
If a patient is experiencing hearing problems refer to Audiology services for a battery of hearing tests.	GPP
A hearing aid trial should be considered although it is often not suitable for this patient population.	GPP
A trial with an FM hearing device is recommended in cases of ataxia with Auditory Neuropathy Spectrum Disorder (ANSD).	C [24, 25]
Refer to hearing therapist or speech and language therapist for guidance on communication tactics.	GPP
For those who do not achieve any benefit from hearing aids, consider a referral to a cochlear implant centre.	D [26]
In specific cases (e.g. ANSD) a referral to a neuro-otologist should be considered.	GPP
4.13 Eye symptoms	
Recommendation	Grade
A referral to a neuro-ophthalmologist is recommended if ataxia patients have any eye symptoms.	GPP
If disabling nystagmus or oscillopsia is present treatment is recommended, often with either gabapentin or baclofen.	B [27–29]
Refer to an optometrist or neuro-ophthalmologist for restoration of single vision with prisms in cases of diplopia.	GPP
Patients with visual impairment should be offered low vision aids and the possibility of having their visual disability registered.	GPP
4.14 Cognition	
Recommendation	Grade

Table 4 Symptomatic treatments *(Continued)*

When cognitive impairment is suspected (even if mild) referral to a Neuropsychology department is recommended.	GPP
Cognitive rehabilitation is recommended for those patients with cognitive impairment.	C [30]
Characterising the course of the cognitive impairment is advisable in order to inform the likely prognosis.	GPP
	GPP
4.15 Depression and other psychiatric symptoms	
Recommendation	Grade
In many cases depression can be treated in primary care using medications, counselling or cognitive behavioural therapy.	GPP
In more severe or complex cases of depression and other psychiatric symptoms a referral to a psychiatrist/ neuropsychiatrist in secondary care is recommended.	GPP
For adults consult NICE Guidelines for the treatment of depression in patients with a chronic physical disorder [10].	GPP

Empfehlungen nicht ärztliche Leistungserbringer:

Table s2: Allied health professional interventions

Recommendation	**Grade**
Referral to a full range of therapies including speech and language therapy (SLT), physiotherapy (PT) and occupational therapy (OT) should be made available to patients with ataxia.	GPP

s2.1 Speech and language therapy

Recommendation	**Grade**
If patients experience specific difficulties with either their communication and/or swallowing a referral to SLT is recommended. An open referral system should be in place where patients are able to access help from SLT as and when required.	GPP
It is important that speech and language therapists (SLTs) undertake a comprehensive assessment of each patient's communication, which takes into consideration the impact of communication difficulties on the individual's activities of daily living and life roles.	GPP
SLTs should be vigilant for any signs of cognitive and/or hearing difficulties in patients with ataxia that might impact on communication, and the management strategy should be modified accordingly.	GPP
In the absence of evidence-based guidance on the most effective treatment, the therapist will need to devise individualised treatment programmes for dysarthria, based on findings of a comprehensive assessment.	GPP
When speech intelligibility levels fall below 50% or when reduced intelligibility has a significant impact on functional communication, alternative and augmentative means of communication should be considered.	D [52]

A comprehensive case history should be taken by the therapist- including the identification of signs and symptoms of dysphagia, detailed current eating and drinking behavior, and individual dietary preferences.	GPP
An instrumental examination of swallowing is indicated when information gained from clinical examination is not sufficient to guide management of the presenting dysphagia.	GPP
A multidisciplinary approach is recommended to dysphagia management between the therapist and dietician, to ensure optimal nutrition and hydration, as well between the therapist and the physiotherapist/occupational therapist to ensure optimal feeding position and use of aids or adaptations *(see table 13 in the full document for dysphagia management techniques).*	GPP
Muscle strengthening exercises can be indicated, and if so they should specifically target underlying swallowing pathophysiology.	GPP

s2.2 Physiotherapy

Recommendation	Grade
Patients with progressive ataxia should be referred to see a physiotherapist or neuro-physiotherapist at an early stage of the disease in order to establish strategies to maintain function (e.g. balance, upper limb coordination, posture) and prevent falls.	GPP
Consider the potential use of rehabilitation approaches and the specific interventions for gait/balance and upper limb tremor for patients with ataxia on a case by case basis.	GPP
Consider suggesting rehearsal of intended steps through eye movement alone, i.e. looking at foot target placement for each step, before negotiating a cluttered room, as it might improve performance and safety.	D [53, 54]
Consider the use of video-game based coordinative programme in children with ataxia who can walk unaided under PT supervision.	C [55]
The use of walking aids is recommended and should be assessed on a case by case basis. Light touch as a balance aid may be helpful for postural orientation and stability.	GPP
Upper extremity weight bearing during ambulation may lead to worsening of gait parameters. It is important, therefore, for people with ataxia to decrease their dependency on weight bearing through the upper limbs (for example, by not leaning on furniture to assist when walking).	GPP
Careful assessment is required when recommending walking aids to patients with dysmetria, dysdiadochokinesia and tremor.	GPP
People with ataxia should be encouraged to exercise as part of health promotion but ensure that risk factors and health and safety considerations are assessed.	GPP
In patients with Friedreich's ataxia and cardiac complications, advice form a cardiologist should be sought before embarking on an exercise program.	GPP
Assess seating position and posture when advising on a wheelchair.	GPP

Physiotherapists should be aware of the spectrum of additional specific impairments that people with progressive ataxia may have, such as fatigue, which also need to be treated.	GPP

s2.3 Occupational therapy

Recommendation	Grade
When it becomes increasingly difficult for people with ataxia to perform everyday activities referral to OT services is recommended.	GPP
OT assessment tools should measure the person's occupational engagement and/or satisfaction with their performance of an activity.	GPP
When making an assessment for treatment and management, therapists should refer to general considerations for intervention in the full guidelines.	GPP
Following a complete OT assessment, when a list of main concerns has been considered and treatment goals prioritised, consult practical suggestions in this section for guidance.	GPP/D
Fatigue management should be considered as part of the OT assessment.	D
Provide information on fatigue and discuss strategies, using activity analysis to help people look at alternative ways of completing tasks in a more energy efficient way.	GPP
Therapists should be mindful of the psychological state of the person with ataxia and refer to counselling or cognitive behavioural therapy as appropriate, and/or consider that anxiety management may be required.	D
Consider the need for future assessments when occupational needs changes and how the patient can re-access both OT and other appropriate services.	GPP

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Klockgether T. et al. 2018 [2].

Deutsche Gesellschaft für Neurologie

Ataxien des Erwachsenenalters, S1-Leitlinie, 2018, in: Deutsche Gesellschaft für Neurologie (Hrsg.), Leitlinien für Diagnostik und Therapie in der Neurologie

<u>Ziele</u> der Leitlinie „Ataxien des Erwachsenenalters“ sind:

- Festlegung eines möglichst standardisierten und kosteneffizienten Vorgehens in der diagnostischen Abklärung von Ataxien im Erwachsenenalter
- Empfehlungen zu allgemeinen und spezifischen Behandlungsmöglichkeiten bei Ataxien
- Verbesserung der Beratung und Betreuung von Patienten mit Ataxie.

Methodik:

Konsensverfahren via Email

Empfehlungen:

„5.2 Friedreich-Ataxie (FRDA)

5.2.3 Spezifische Therapie

Die Kardiomyopathie ist nach allgemeinen kardiologischen Maßgaben zu therapieren.

Der Diabetes mellitus ist in der Regel nach kurzem Erkrankungsverlauf insulinpflichtig.

Die Indikation zur operativen Korrektur einer Skoliose muss individuell erfolgen. Operationen von Hohlfußbildungen sind in der Regel nicht empfehlenswert.

Eine antioxidative Therapie mit Idebenone hatte in zwei randomisierten kontrollierten Phase-III-Studien in einer Dosis bis zu 45 mg/kg/Tag oral bei jugendlichen und erwachsenen FRDA-Patienten über eine Behandlungsdauer von sechs bzw. zwölf Monaten keine Wirkung auf die Ataxie oder die Kardiomyopathie (Lynch et al. 2010). Eine spezifische Therapie steht somit für die FRDA weiterhin nicht zur Verfügung.

Ein medikamentöser Behandlungsversuch mit Riluzol (2 x 50 mg/Tag oral) ist vertretbar.“

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2022) am 23.08.2022

#	Suchfrage
1	MeSH descriptor: [Friedreich Ataxia] explode all trees
2	Friedreich*:ti,ab,kw AND (ataxia* OR disease*):ti,ab,kw
3	FRDA:ti,ab,kw
4	(Hereditary AND ataxia*):ti,ab,kw
5	(Hereditary AND Spinal AND Scleros*):ti,ab,kw
6	Frataxin:ti,ab,kw
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	MeSH descriptor: [Spinocerebellar Degenerations] explode all trees
9	(Cerebellar OR Spinocerebellar OR Spino-Cerebellar):ti,ab,kw AND (ataxia* OR degeneration* OR disease*):ti,ab,kw
10	#7 OR #8 OR #9
11	# with Cochrane Library publication date from Aug 2017 to present

Systematic Reviews in PubMed am 23.08.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	friedreich ataxia[MeSH Terms]
2	Friedreich*[tiab] AND (ataxia*[tiab] OR disease*[tiab])
3	FRDA[tiab]
4	Hereditary[tiab] AND ataxia*[tiab]
5	Hereditary[tiab] AND Spinal[tiab] AND Scleros*[tiab]
6	Frataxin[tiab]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	Spinocerebellar Degenerations[MeSH Terms]
9	(Cerebellar[tiab] OR Spinocerebellar[tiab] OR Spino-Cerebellar[tiab]) AND (ataxia*[tiab] OR degeneration*[tiab] OR disease*[tiab])
10	#7 OR #8 OR #9
11	(#10) 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

#	Suchfrage
	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]))))))
12	(#11) AND ("2017/08/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 23.08.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	friedreich ataxia[MeSH Terms]
2	Friedreich*[tiab] AND (ataxia*[tiab] OR disease*[tiab])
3	FRDA[tiab]
4	Hereditary[tiab] AND ataxia*[tiab]
5	Hereditary[tiab] AND Spinal[tiab] AND Scleros*[tiab]
6	Frataxin[tiab]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6

#	Suchfrage
8	Spinocerebellar Degenerations[MeSH Terms]
9	(Cerebellar[tiab] OR Spinocerebellar[tiab] OR Spino-Cerebellar[tiab]) AND (ataxia*[tiab] OR degeneration*[tiab] OR disease*[tiab])
10	#7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
12	(#11) AND ("2017/08/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.08.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO