Neue Leitlinien für die Behandlung der ALS EAN (European Academy of Neurology)

Prof. Dr. Markus Weber

Nationaler ALS Tag

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GUIDELINES

European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD)

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Therapie bei ALS

PICO

Akronym [Bearbeiten | Quelltext bearbeiten]

PICO steht als Akronym für:[3]

Population oder Patient, Problem:

Beschreibung der Gruppe von Patienten bzw. des Problems

Intervention = Technologien, diagnostisches/therapeutisches Verfahren:

Welche Intervention ist Gegenstand der gegenwärtigen Untersuchung?

Comparison oder Control = Vergleichsintervention:

Was ist die Hauptalternative, mit der die Intervention verglichen werden kann?

Outcome = Zielgröße:

Was soll erreicht werden?

Bsp.:What is the effectiveness of pharmacological interventions for muscle cramps in people with ALS?

Strong recommendation in favour	For most patients the benefits outweigh the harms. This means that all or virtually all, patients will want and benefit from the recommended intervention. Represented as ++ in the text.
Weak recommendation in favour	It is less clear that the benefits outweigh the harms. Many patients would still benefit and prefer the recommended intervention, but there may be greater individual variation. Represented as + in the text.
Weak recommendation against	It is less clear that the harms outweigh the benefits. Many patients would not benefit and for the intervention, but there may be greater individual variation. Represented as ¬ in the text.
Strong recommendation against	For most patients the harms outweigh the benefits. This means that all or virtually all, patients will not want and will not benefit from the intervention. Represented as ¬ ¬ in the text.

https://doi.org/10.1093/brain/awab472 BRAIN 2022: 145; 1207–1210 | 1207

BRAIN
SPECIAL COMMENTARY

The importance of offering early genetic testing in everyone with amyotrophic lateral sclerosis

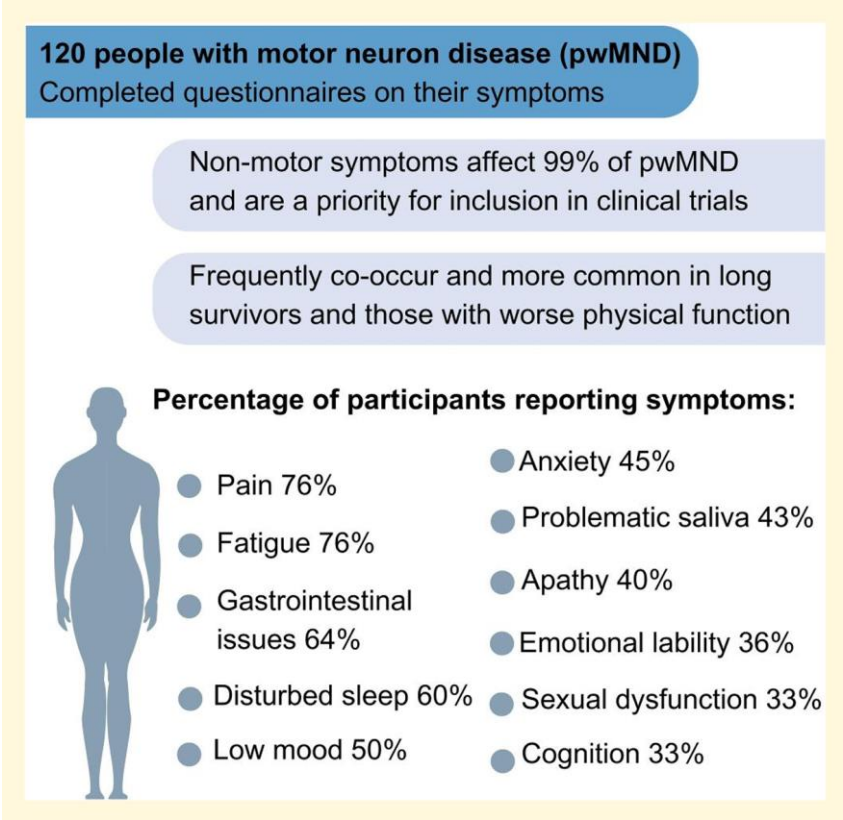
Disease- modifying therapies Recommendations

- **Riluzole (Rilutek)**
  - *Offer* lifelong riluzole to all people with ALS at diagnosis. [++]
- **Edaravone (Radicava)**
  - Based on the available evidence, the panel currently *does not recommend* the use of intravenous or oral edaravone outside the context of a trial. [– –]
- **Cell-based therapies (Stammzellen)**
  - The panel *cannot recommend* the use of cell- based treatments outside the context of clinical trials. [– –]
- **AMX0035 (Relyvrio)**
  - Based on the available evidence, the panel *does not currently recommend* the use of AMX0035 outside the cotext of a clinical trial. [–]
- **Tofersen**
  - In patients with progressive ALS caused by pathogenic mutations in superoxide dismutase 1 (SOD1), *offer tofersen as first- line treatment*. [++]

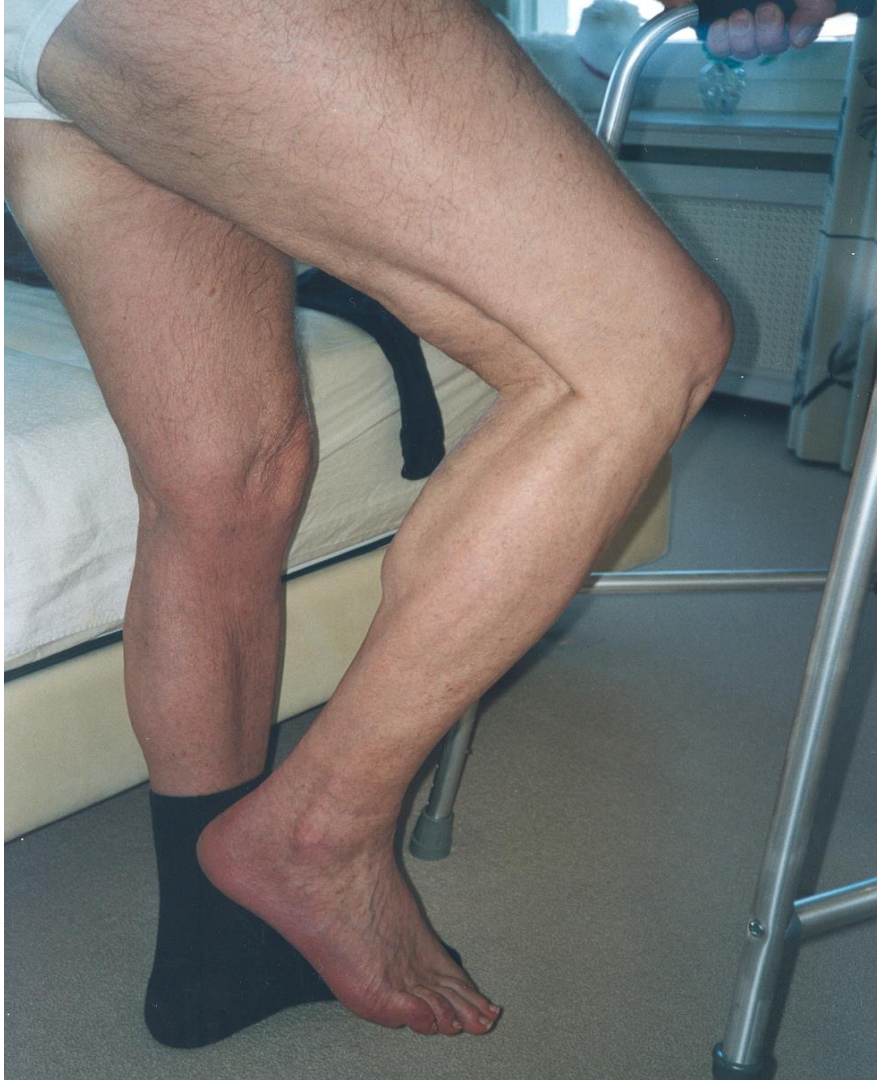
https://doi.org/10.1093/braincomms/fcad336 E. Beswick et al. BRAIN COMMUNICATIONS 2024: Page 1 of 17 | 1

BRAIN COMMUNICATIONS

Non-motor symptoms in motor neuron disease: prevalence, assessment and impact



Krampf



Natrium Kanal Blocker bei ALS Krämpfen

ARTICLES

Neurology® 2016;86:1474-1481

A randomized trial of mexiletine in ALS

Safety and effects on muscle cramps and progression

Mexiletine 300 mg und 900 mg/Tag ist sicher

1/3 mit 900 mg Einnahme gestoppt wegen Nebenwirkungen

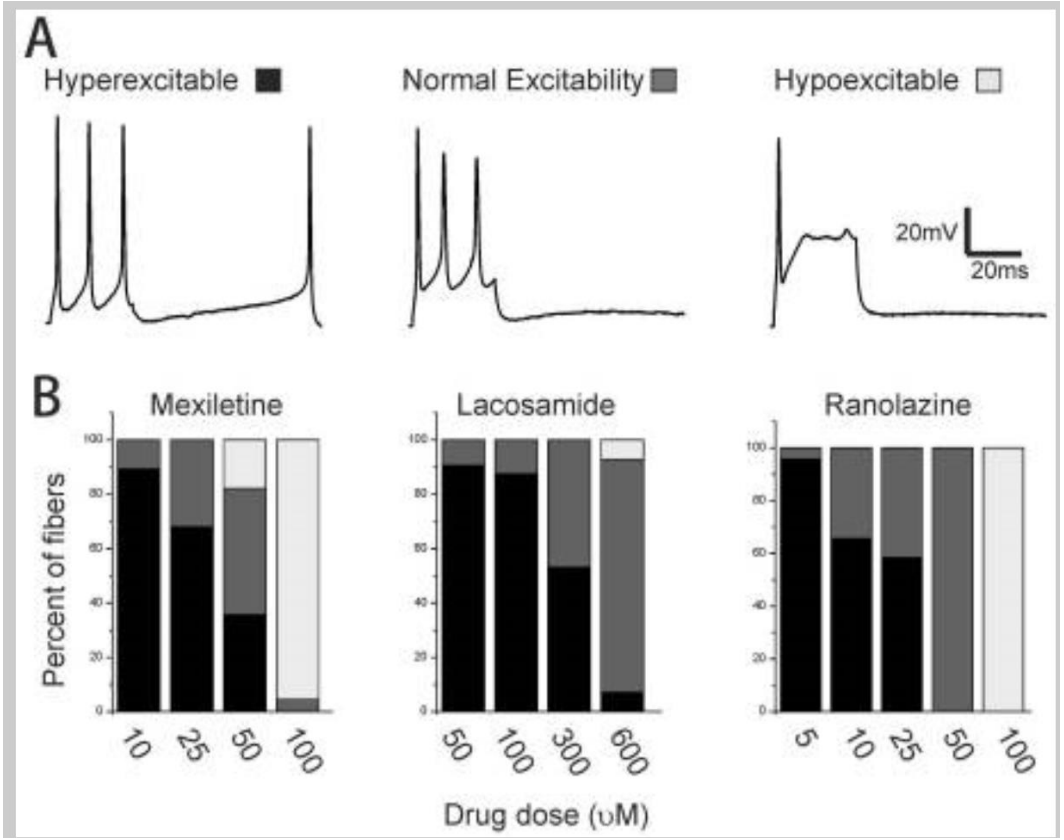
Dosis-abhängige Reduktion der Krampfhäufigkeit und-stärke

Mit 300 mg Abnahme:

Häufigkeit	31%
Stärke	45%

Kosten in Europe (~ 500 Euro/Monat)

Sodium channel slow inactivation as a therapeutic target for myotonia congenita (Novak et al. 2015)



Ranolazin (Ranexa) bei Myotonia congenita

Neurology. 2017 Aug 15;89(7):710-713. doi: 10.1212/WNL.0000000000004229. Epub 2017 Jul 14.

Open-label trial of ranolazine for the treatment of myotonia congenita.

Arnold WD[1], Kline D[2], Sanderson A[2], Hawash AA[2], Bartlett A[2], Novak KR[2], Rich MM[2], Kissel JT[2].

Author information

Abstract

OBJECTIVE: To determine open-label, pilot study whether ranolazine could improve signs and symptoms of myotonia and muscle stiffness in patients with myotonia congenita (MC).

METHODS: Thirteen participants were assessed at baseline and 2, 4, and 5 weeks. Ranolazine was started after baseline assessment (500 mg twice daily), increased as tolerated after week 2 (1,000 mg twice daily), and maintained until week 4. Outcomes included change from baseline to week 4 in self-reported severity of symptoms (stiffness, weakness, and pain), Timed Up and Go (TUG), hand grip and eyelid myotonia, and myotonia on EMG.

RESULTS: Self-reported severity of stiffness ($p < 0.0001$) and weakness ($p < 0.01$) was significantly improved compared with baseline. TUG and grip myotonia times were reduced ($p = 0.03$, $p = 0.01$). EMG of the abductor digiti minimi and tibialis anterior showed significantly reduced myotonia duration ($p < 0.001$, $p < 0.01$) at week 4. No participant discontinued ranolazine because of side effects.

CONCLUSIONS: Ranolazine appeared to be well tolerated over a period of 4 weeks in individuals with MC, and ranolazine resulted in improvement of signs and symptoms of muscle stiffness. The findings of this study suggest that ranolazine should be investigated in a larger controlled study.

CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that ranolazine improves myotonia in myotonia congenita.

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DOI: 10.1002/mus.27560

CLINICAL RESEARCH SHORT REPORTS

MUSCLE&NERVE WILEY

Open-label pilot study of ranolazine for cramps in amyotrophic lateral sclerosis

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Abstract

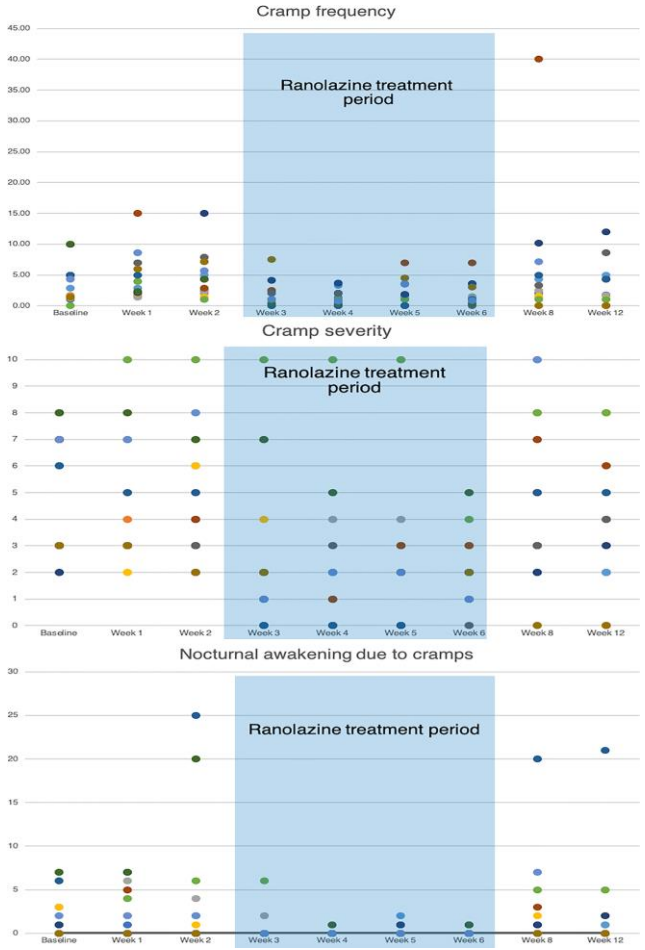
Introduction/Aims: Neuronal hyperexcitability (manifested by cramps) plays a pathological role in amyotrophic lateral sclerosis (ALS), and drugs affecting it may help symptomatic management and slow disease progression. We aimed to determine safety and tolerability of two doses of ranolazine in patients with ALS and evaluate for preliminary evidence of drug-target engagement by assessing muscle cramp characteristics.

Methods: We performed an open-label dose-ascending study of ranolazine in 14 individuals with ALS in two sequential cohorts: 500 mg (cohort 1) and 1000 mg (cohort 2) orally

Open-label pilot study of ranolazine for cramps in amyotrophic lateral sclerosis

Muscle and Nerve, Volume: 66, Issue: 1, Pages: 71-75

Cramp frequency, cramp severity, and nocturnal awakenings



EAN Guidline 6b. Muscle cramps

- Consider sodium blockers (ranolazine, quinine sulfate, mexiletine, carbamazepine), gabapentine, pregabalin, and baclofen for the management of cramps as symptomatic treatment. [+]
- Start quinine sulfate at low doses (100 to 200 mg per day) and monitor for cardiac adverse events before and after prescription. [++]

Emotionale Labilität, Speichelfluss, Sprech- und Schluckstörung

Neurotherapeutics (2017) 14:762–772
DOI 10.1007/s13311-016-0508-5

ORIGINAL ARTICLE

Enhanced Bulbar Function in Amyotrophic Lateral Sclerosis: The Nuedexta Treatment Trial

Richard Smith[1] · **Erik Pioro**[2] · **Kathleen Myers**[1] · **Michael Sirdofsky**[3] · **Kimberly Goslin**[4] · **Gregg Meekins**[5] · **Hong Yu**[6,7] · **James Wymer**[8] · **Merit Cudkowicz**[6,7] · **Eric A. Macklin**[6,7] · **David Schoenfeld**[6,7] · **Gary Pattee**[9]

"hausgemacht" (Spitalpharmazie):
Chinidinsulfat 0.9.% Suspension + Dextromethorphan (Hustensaft)

Published online: 9 January 2017

Abstract The goal of this randomized, blinded, crossover clinical trial was to determine whether Nuedexta (dextromethorphan and quinidine) enhanced speech, swallowing, and salivation in patients with ALS. Sixty patients with amyotrophic lateral sclerosis (ALS) received either Nuedexta or placebo for 28 to 30 days, followed by a 10 to 15-day washout period. Subsequently, patients were switched to the opposite treatment arm for the remaining days of the trial. The primary endpoint was a reduction in the self-report Center for Neurologic Study Bulbar Function Scale (CNS-BFS) score. The rater-administered ALS Functional Rating Scale Revised was the principal secondary endpoint. The CNS-BFS score improved with active treatment, decreasing from a mean of 59.3 in the placebo arm of the trial to 53.5 during the drug-treatment arm ($p < 0.001$). Each of the individual domains of bulbar function interrogated by the CNS-BFS responded to treatment with Nuedexta as follows: salivation: 15.8 *versus* 14.3 ($p = 0.004$); speech: 24.6 *versus* 22.2 ($p = 0.003$); swallowing: 18.9 *versus* 17.1 ($p = 0.009$). Similarly, the bulbar component of the ALS Functional Rating Scale Revised im-

Electronic supplementary material The online version of this article

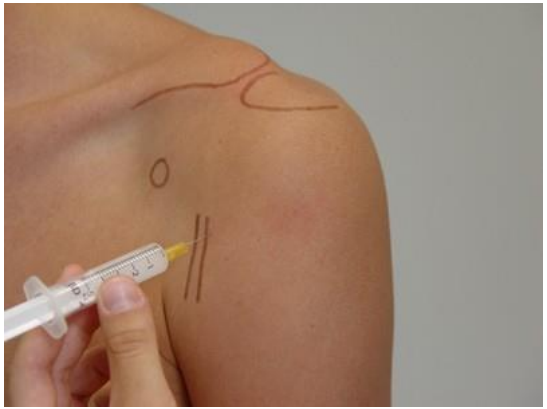
EAN Guideline 6j.Insomnia (Schlafstörung)

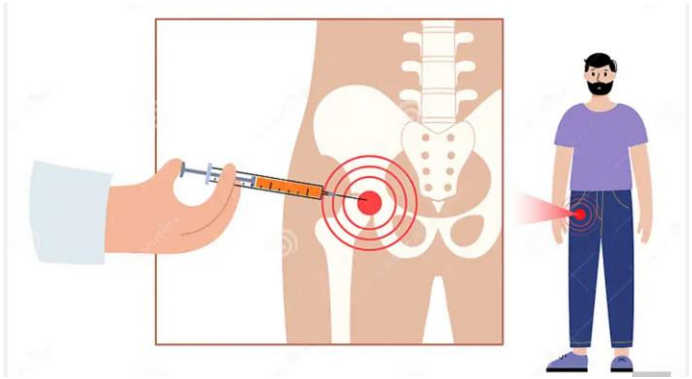
In people with ALS who experience sleep difficulties, identify and treat the underlying cause. For example:

- Anxiety
- Respiratory insufficiency
- Pain
- Muscle cramps
- Emotional distress, depression
- Sleep apnoea
- Inability to move/deficient spontaneous mobility at sleep
- Restless legs syndrome (jedes unangenehme Gefühl: schlimmer in der 2. Tageshälfte/Nachts; nie beim Erwachen, rasche Besserung durch Bewegung)
- Nocturia
- Stiffness. [++]

EAN Guideline 6d. Pain

- **Actively assess for pain. [++]**
- identify and treat the cause or combination of causes (e.g., cramps, spasticity, malpositioning, frozen shoulder, stiff joints, joint immobility, pressure on the joint, sores on the skin, discomfort due to restless legs syndrome). [++]
- For the management of joint pain, consider targeted steroid injections. [+]



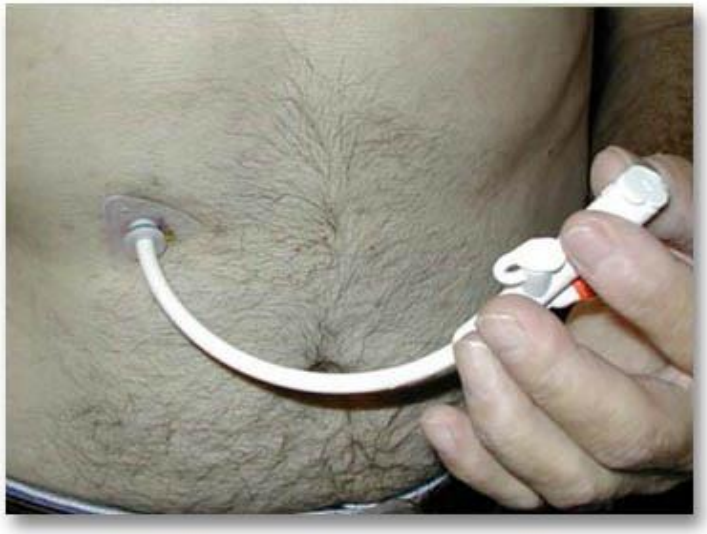


Locher, H. Therapeutische Injektionen im Schulterbereich. Manuelle Medizin 47, 434–441 (2009)

https://de.dreamstime.com

EAN Guideline Chapter 4. Nutrition (Ernährung)

- Discuss gastrostomy at an **early stage**, and at regular intervals
- taking into account the person's preferences and issues, such as ability to swallow, weight loss, respiratory function, effort of feeding and drinking, and risk of choking.
- Be aware that **some people will not want to have a gastrostomy.** [++]
- In case of respiratory insufficiency, first introduce NIV (Nicht-invasive Heimventilation)



5c. Respiratory insufficiency (Atemschwäche)

- NIV (Non-invasive) ventilation (Heimventilation) should be offered to all patients with ALS with either symptoms, signs, or laboratory investigations supportive of respiratory insufficiency. [++]
  - Erste Symptome
    - Frühmorgendliche Kopfschmerzen
    - Fehlende Erholung durch Nachtschlaf
    - Tagesmüdigkeit/Abgeschlagenheit

Somsak Bumroongwong / EyeEm / Getty Images

Conclusion: The landscape of ALS therapies is rapidly changing…