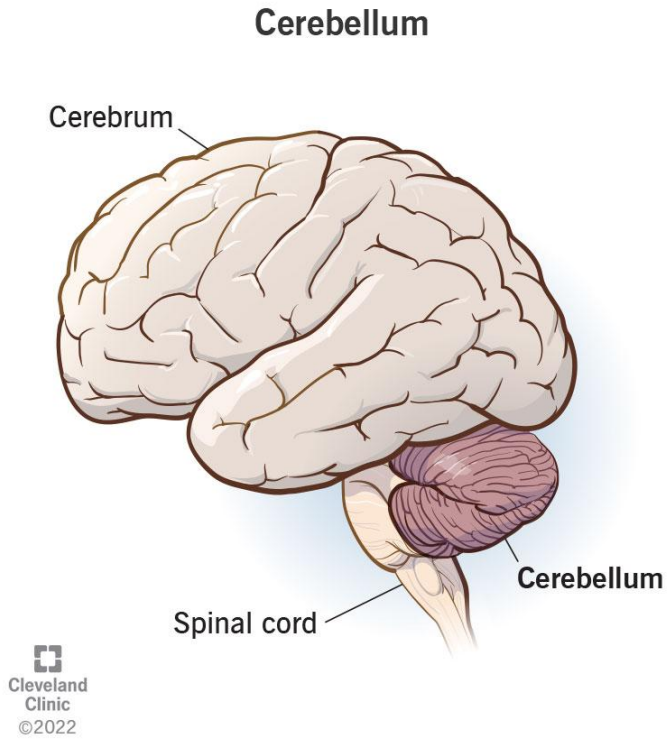
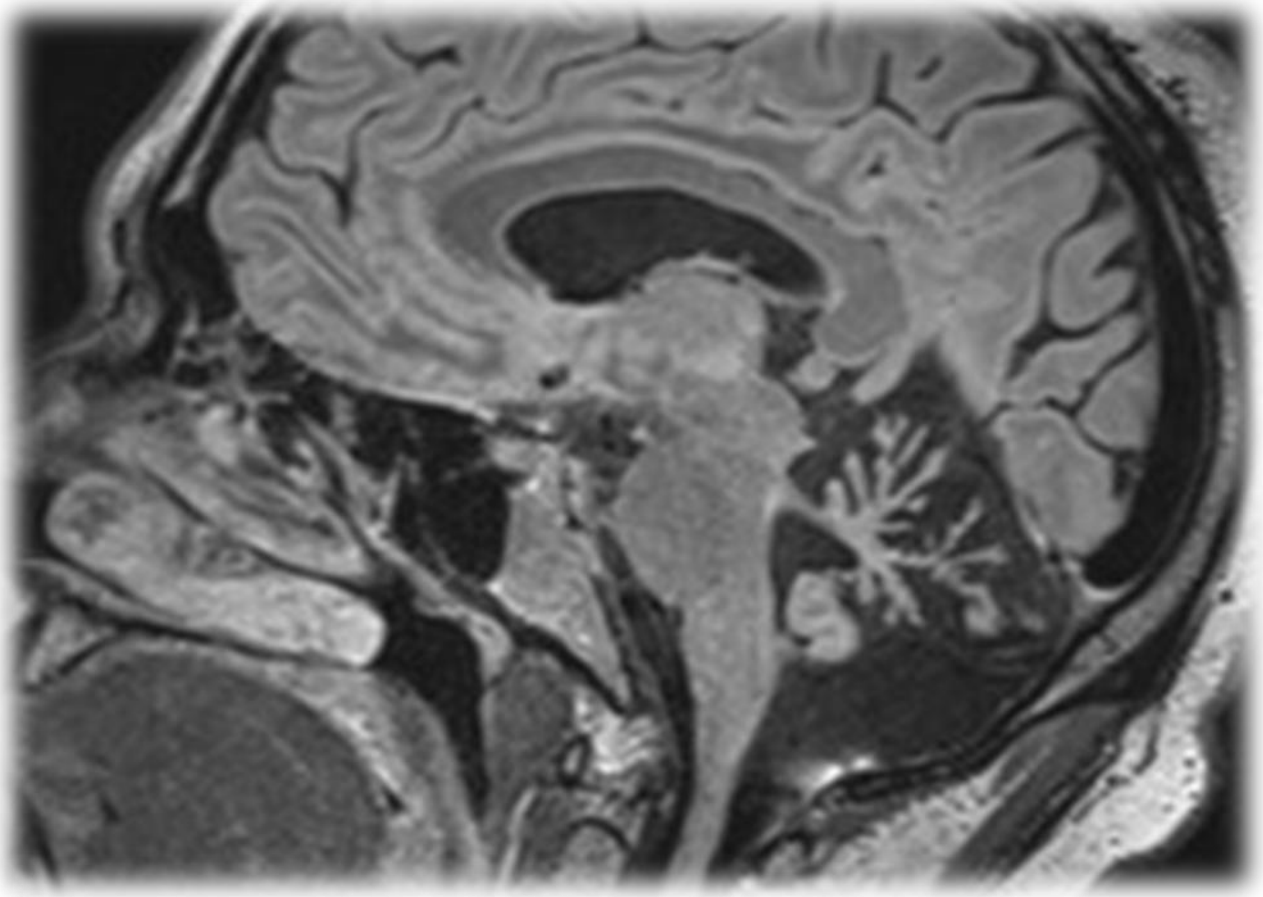




Treatable Cerebellar Ataxias

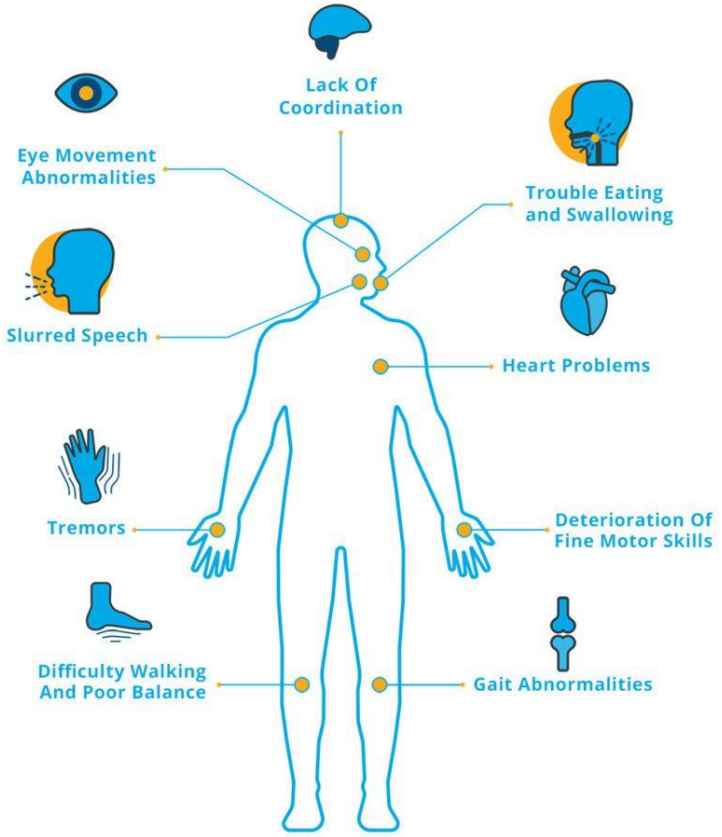
Siegfried Hirczy, M.D.

Assistant Professor, Movement Disorders Section

UT Southwestern Medical Center

What is Cerebellar Ataxia?

- Definition
  - A set of diseases characterized by cerebellar dysfunction which manifests as impaired coordination of motor* performance
- Etiologies
  - Genetic
  - Nutritional
  - Autoimmune
  - Paraneoplastic
  - Infectious



What does it mean for a disorder to be treatable?

- Definition of Treatable
  - Capable of being treated : yielding or responsive to treatment
- Levels of Treatment Effect
  - Restorative (Return to Healthy State)
  - Curative (Resolution of Causative Derangement)
  - Symptomatic (Reduction of Disease Related Dysfunction)
  - Supportive (Reduction of Disease Related Functional Impairment)

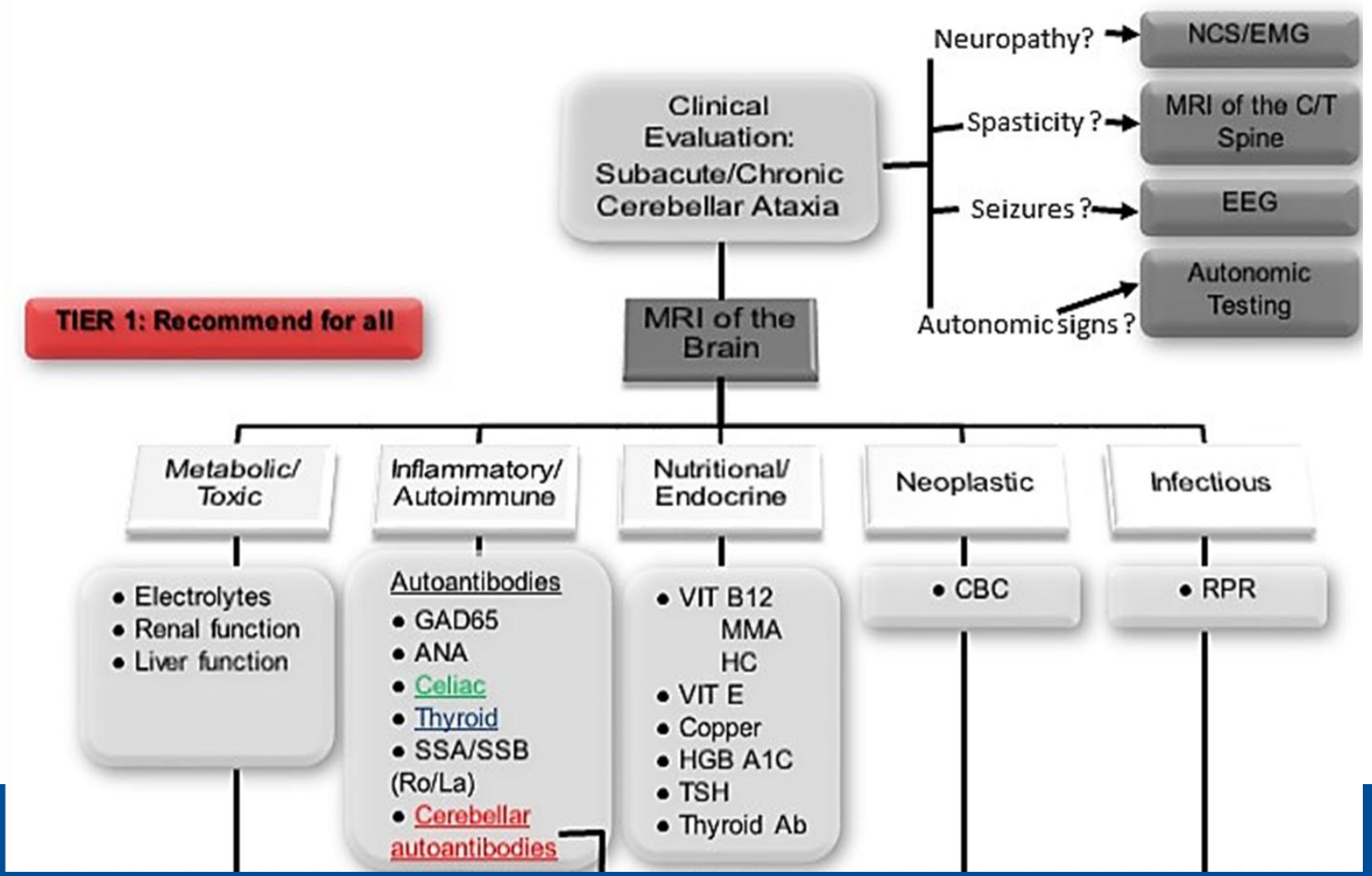
What is there to treat in ataxia?

1) Cause
2) Ataxic Features
   - Gait dysfunction and imbalance
   - Clumsiness and fine motor deficits
   - Dysarthria
   - Diplopia and visual disturbances
3) Non-ataxic Features
   - Spasticity, Rigidity, and Dystonia
   - Tremors and Parkinsonism
   - Neuropathy
   - Cognitive changes
   - Psychiatric changes

Quick Review on the Diagnosis of Ataxia

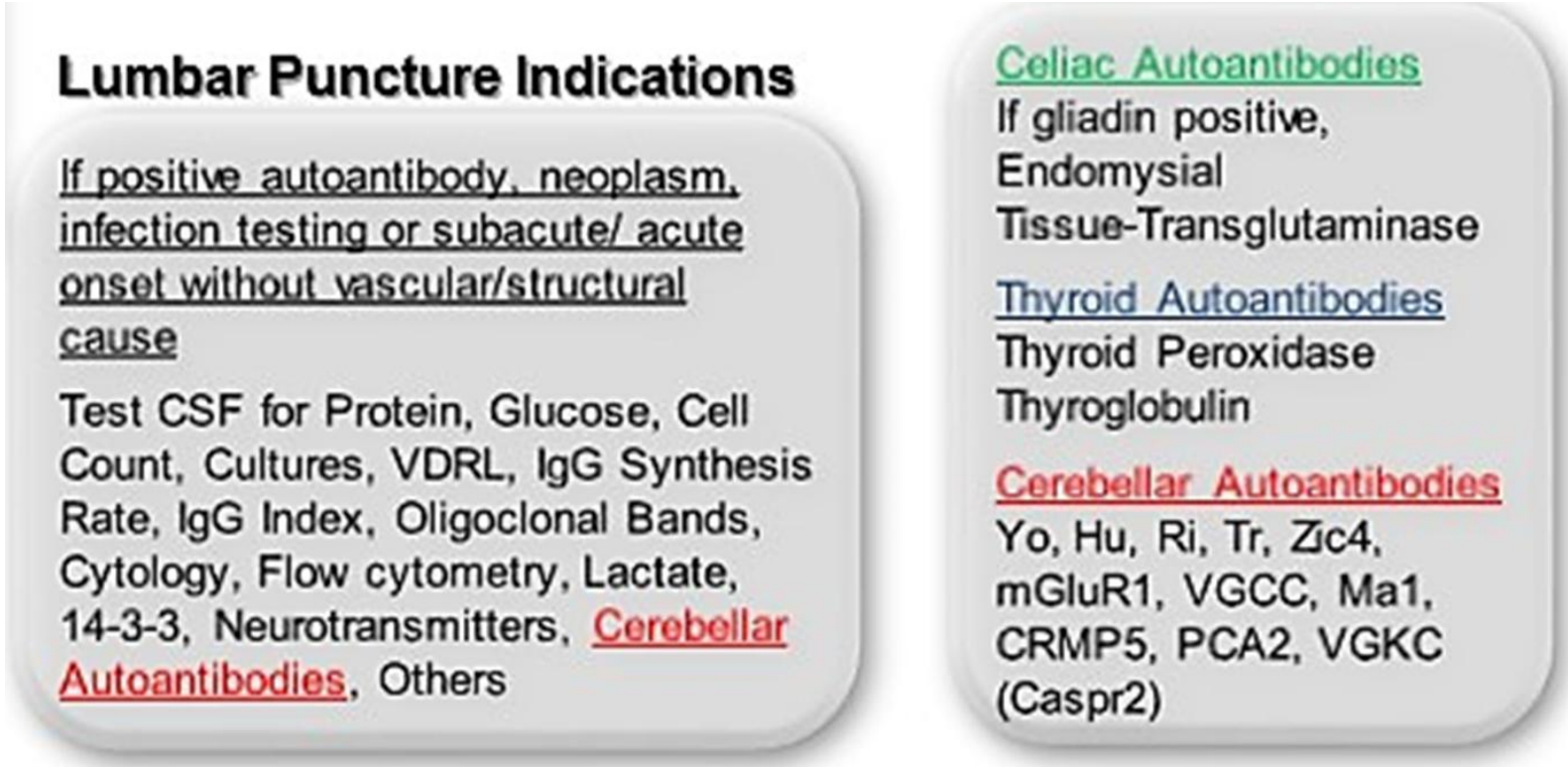
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Where to start?



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Lumbar puncture?



Genetic testing?

Step 1
Test repeat-associated ataxias first-SCA3, SCA2, SCA6, and SCA1 account for 50-60% of dominant ataxia.
Friedreich ataxia: 5-10%
RFC1-associated ataxia may be as common as FA
SCA27B may be the most common inherited ataxia

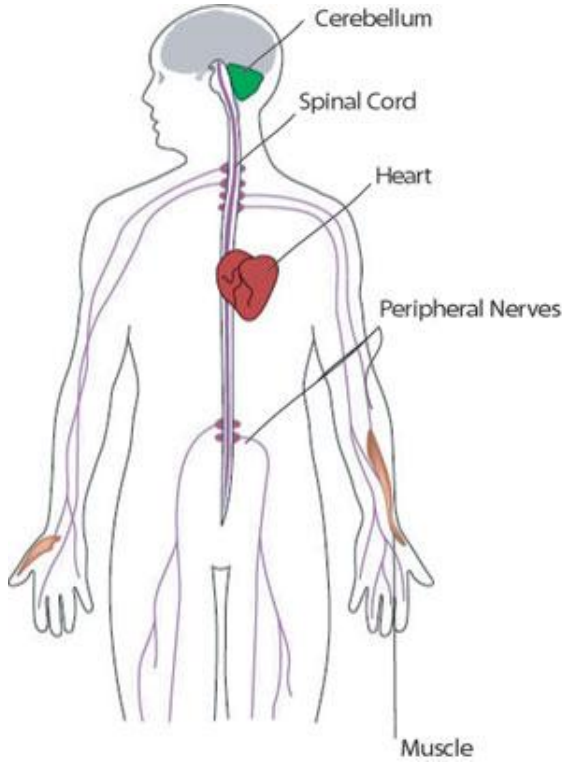
Step 2
Exome sequencing based approaches, either expanded panels or whole exome

Treatments for Specific Cerebellar Ataxias

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Friedrich's Ataxia

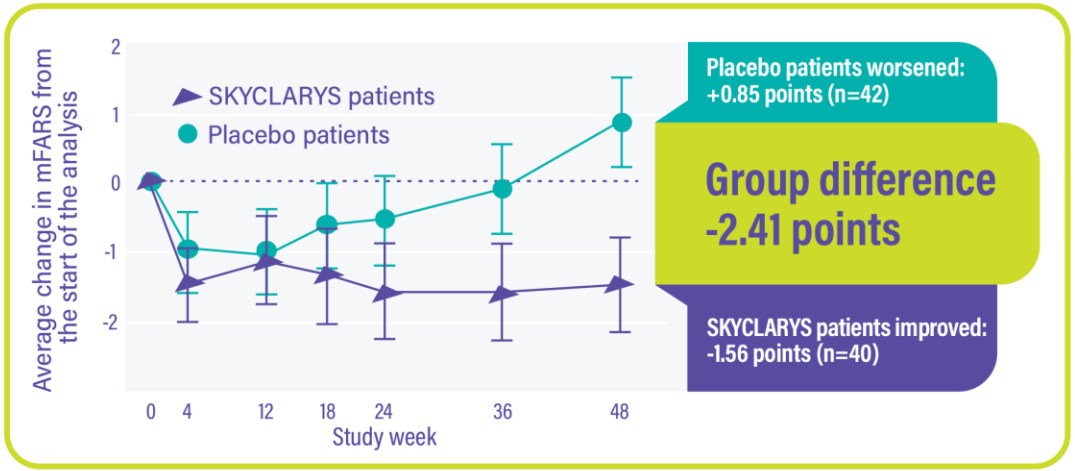
- Etiology
  - Biallelic intronic GAA expansion in FXN gene, resulting in reduced frataxin (AR)
  - Disruption of biosynthesis, iron dysregulation, mitochondrial dysfunction
- Clinical Presentation
  - Young onset
  - Ataxia
  - Neuropathy (Pes Cavus)
  - Cardiac dysfunction
  - Diabetes



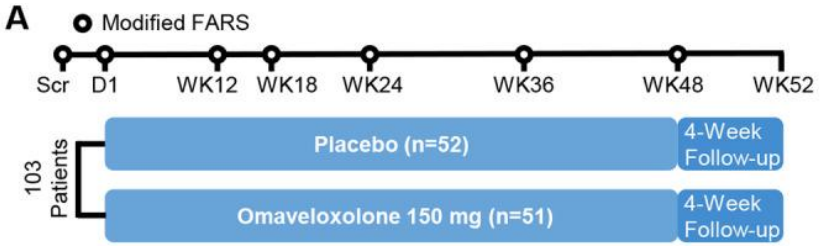
MDA Website, 11/2026

Omaveloxolone (SKYCLARYS) – Approval 2023

- Mechanism
  - Nrf2 activation
  - Improves mitochondrial function and reduces inflammation

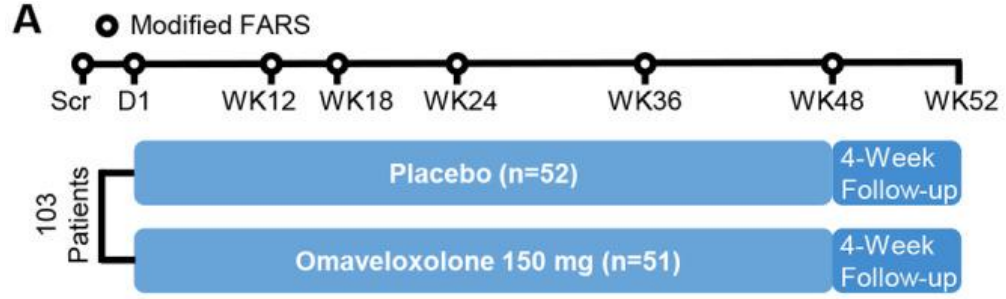


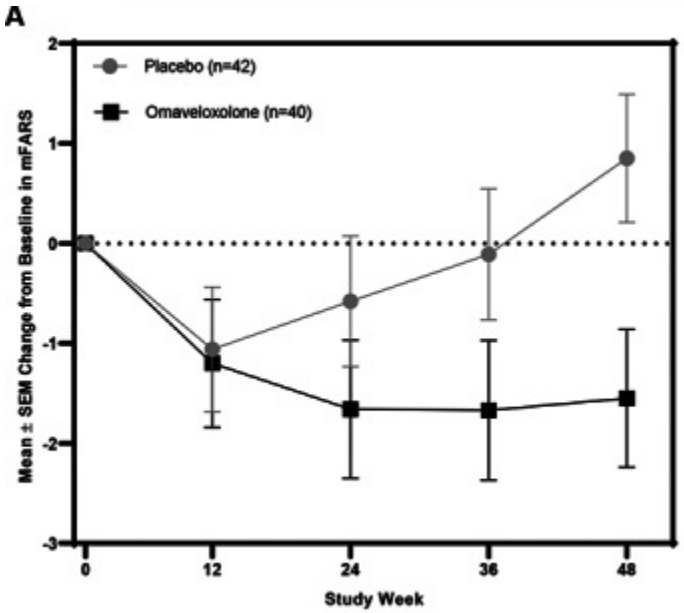
- Evidence (MOXIe)
  - DB-RCT, N = 40/42



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MOXIe





Adverse reactions	SKYCLARYS (n=51)	Placebo (n=52)
Elevated liver enzymes (AST/ALT)	37%	2%
Headache	37%	25%
Nausea	33%	13%
Abdominal pain	29%	6%
Fatigue	24%	14%
Diarrhea	20%	10%
Musculoskeletal pain	20%	15%
Oropharyngeal pain	18%	6%
Influenza	16%	6%
Vomiting	16%	12%
Muscle spasms	14%	6%
Back pain	13%	8%
Decreased appetite	12%	4%
Rash	10%	4%

Niemann-Pick Type C

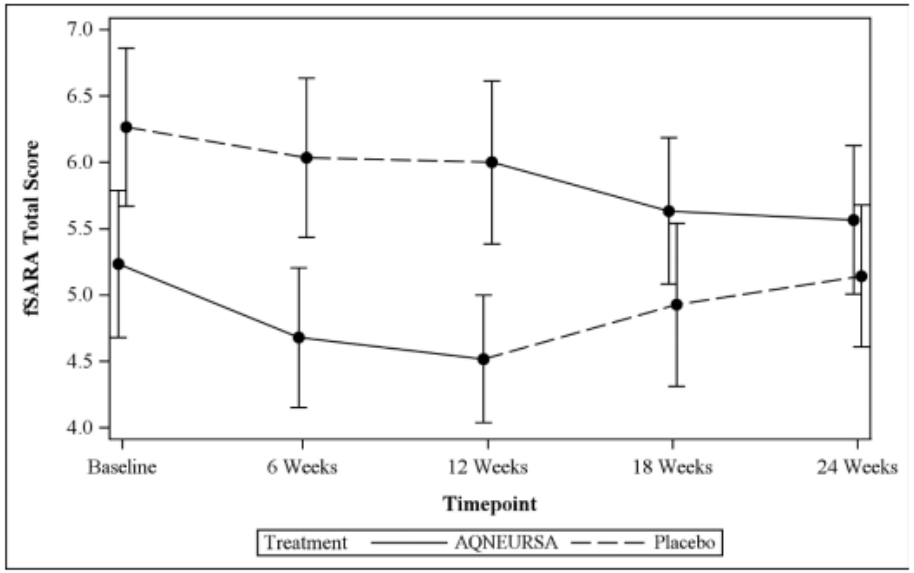
- Etiology
  - Biallelic intronic GAA expansion in FXN gene, resulting in reduced frataxin (AR)
  - Disruption of biosynthesis, iron dysregulation, mitochondrial dysfunction
- Clinical Presentation
  - Childhood onset, though can occur in adulthood
  - Ataxia
  - Supranuclear gaze palsy
  - Cognitive impairment
  - Epilepsy

MDA Website, 11/2026

Levacetylleucine (AQNEURSA) – Approved 2024

- Mechanism
  - Unknown, upregulates HSP70 reducing cellular stress and lysosomal function
- Evidence (NCT05163288)
  - DB-RCT, Cross-over, N = 30/30

Figure 1: Mean (+/- standard error) Plot of the fSARA Total Score by Time and Treatment Sequence in Adult and Pediatric Patients with NPC (Trial 1)

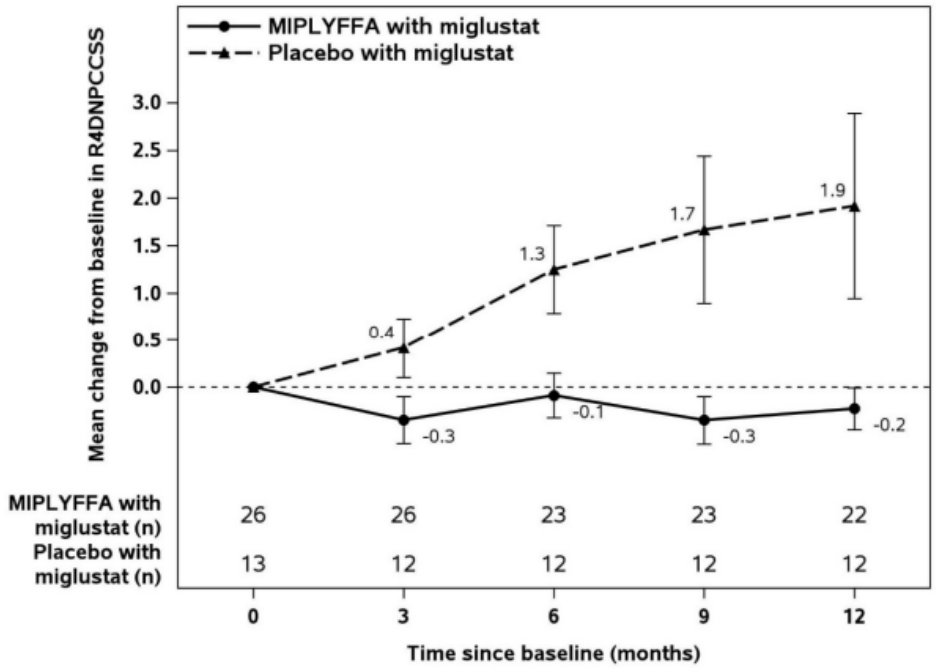


FDA Package Insert

Arimoclomol (Miplyffa) – Approved 2024

- Mechanism
  - Stimulation of cellular repair and activation of chaperons (HSP70)
- Use
  - Must be used in combination with miglustat
- Evidence
  - DB-RCT, N = 28/22

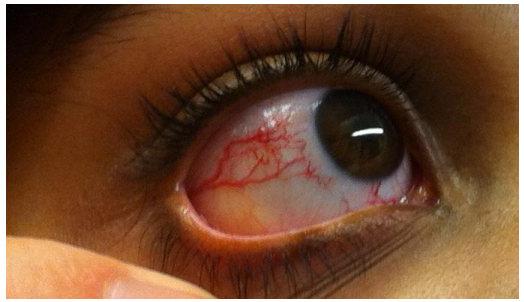
Figure 1: MIPLYFFA and Placebo Mean Change from Baseline (± SE) in R4DNPCCSS Score Over Time in Patients 2 to 19 Years of Age with NPC Who Also Received Miglustat (Trial 1)

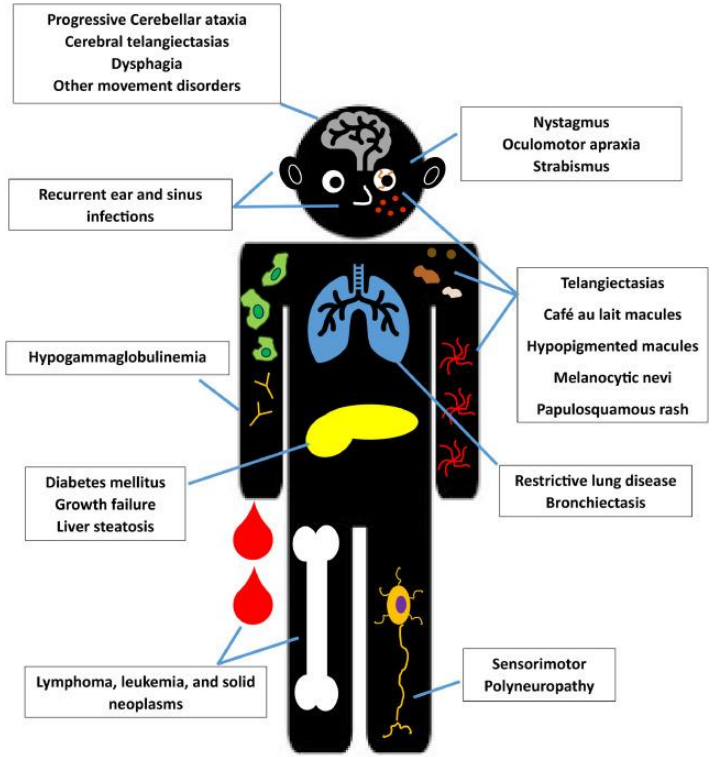


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Ataxia-Telangiectasia (A-T)

- Etiology
  - ATM gene mutation
- Clinical Presentation
  - Childhood onset
  - Autosomal recessive
  - Ataxia
  - Telangiectasias
  - Recurrent infections
  - Neoplasms





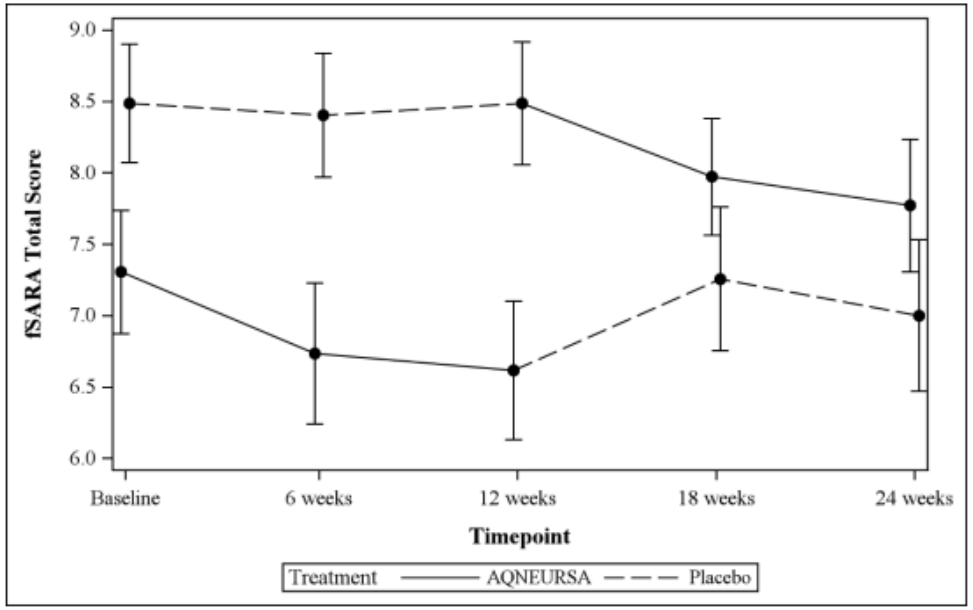
Collyer, etal (2024)

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Levacetylleucine (AQNEURSA) – Approved 2026

- Mechanism
  - Unknown, upregulates HSP70 reducing cellular stress and lysosomal function
- Evidence (NCT06673056)
  - DB-RCT, Cross-over, N = 36/37

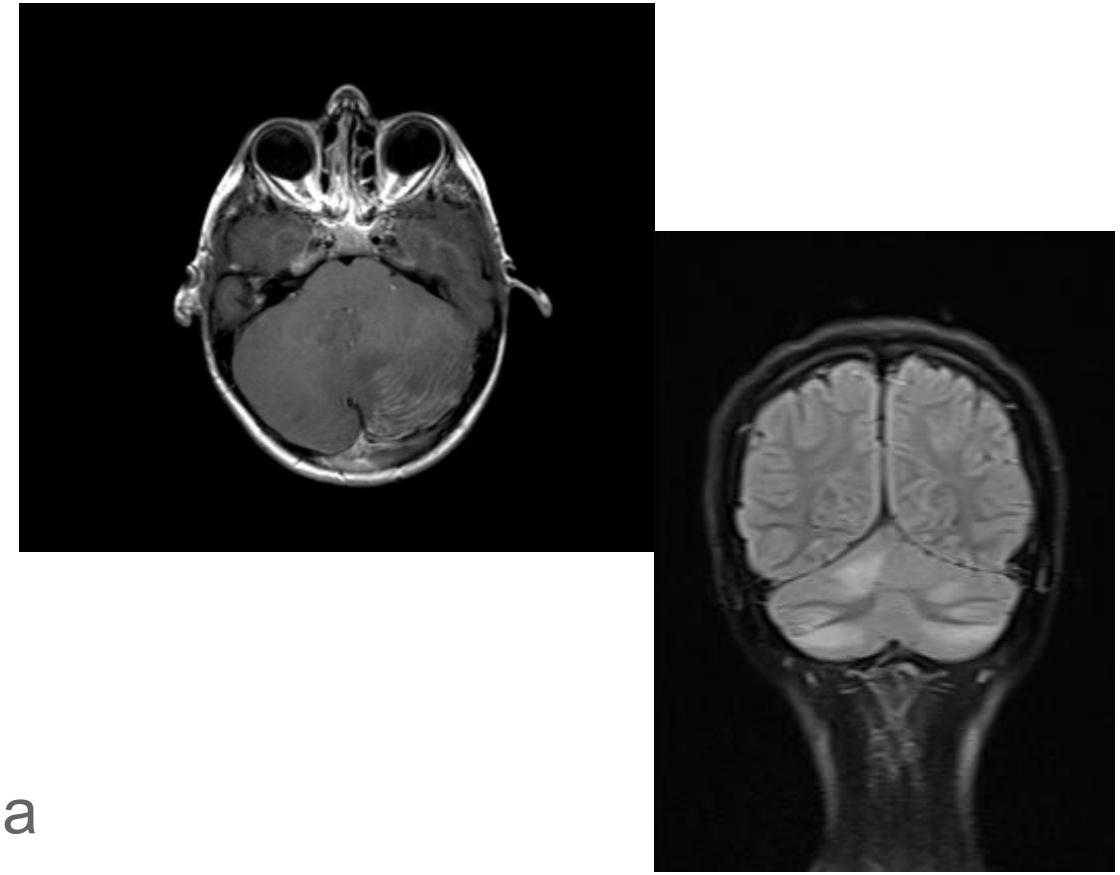
Figure 2: Mean (+/- standard error) Plot of the fSARA Total Score by Time and Treatment Sequence in Adult and Pediatric Patients with A-T (Trial 2)



FDA Package Insert

Immune Mediated Cerebellar Ataxias

- Etiology
  - Immune autoreactivity to cerebellar epitopes
- Types
  - Gluten ataxia
  - Paraneoplastic cerebellar degeneration
  - Anti-glutamate decarboxylase 65 associated
  - Primary autoimmune cerebellar ataxia
  - Post-infectious



Immune Mediated Cerebellar Ataxias: Treatments

- Removal of provoking antigen (tumor, gluten, etc)
- Immunomodulatory
  - First line
    - IVMP 1 g for 3-5 days + taper over 3-6 months
    - IVIG 400 mg/kg/d for 5 days
    - PLEX
  - Second line
    - Rituximab
    - Cyclophosphamide
  - Maintenance
    - Rituximab, MMF, IVIg, AZA, Cyclophosphamide

Gluten Elimination

Clinical Trial > J Neurol Neurosurg Psychiatry. 2003 Sep;74(9):1221-4.
doi: 10.1136/jnnp.74.9.1221.

Dietary treatment of gluten ataxia

M Hadjivassiliou [1], G A B Davies-Jones, D S Sanders, R A Grünewald

Affiliations + expand

PMID: 12933922 PMCID: PMC1738682 DOI: 10.1136/jnnp.74.9.1221

- Methods
  - Pragmatic prospective cohort
  - Adherent to gluten free diet vs not
  - Gluten ataxia definition - positive antigliadin antibodies, exclusion of other etiologies)

- Results
  - 26 adherent and no anti-gliadin
  - 14 control/non-adherent

Table 2 Results of ataxia tests when comparing the treatment and the control groups

Test	GA treatment group (n=26)		GA control group (n=14)		p Value of interaction
	Baseline	One year	Baseline	One year	
Computerised finger-nose test latency (ms)	3296 (1133)	2503 (717)	3372 (1694)	3716 (2066)	0.0001
Hand tapping	80 (32)	89 (33)	59 (28)	50 (19)	0.0002
Foot tapping	79 (37)	95 (41)	78 (29)	72 (26)	0.0001
Peg board, time to fill (s)	291 (146)	248 (80)	410 (201)	496 (292)	0.0015
Quantitative Romberg's test	18 of 26 patients improved		None of 14 improved		0.0001 by χ^2 test
Patients' global clinical impression	0.41 (0.18)	0.62 (0.25)	0.39 (0.15)	0.31 (0.14)	0.0002

Values are mean (SD).
Statistical analysis is by repeated measures analysis of variance except where stated.
GA, gluten ataxia.

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Other Treatable Specific Conditions with Ataxia

Disorder with ataxia	Treatment
Abetalipoproteinemia and hypobetalipoproteinemia	Vitamin E
Biotinidase deficiency	biotin supplementation
Cerebrotendinous xanthomatosis	chenodeoxycholic acid
Coenzyme Q10 deficiency	coenzyme Q10
Hartnup disease	nicotinamide

Current Trials on Pharmacologic Interventions

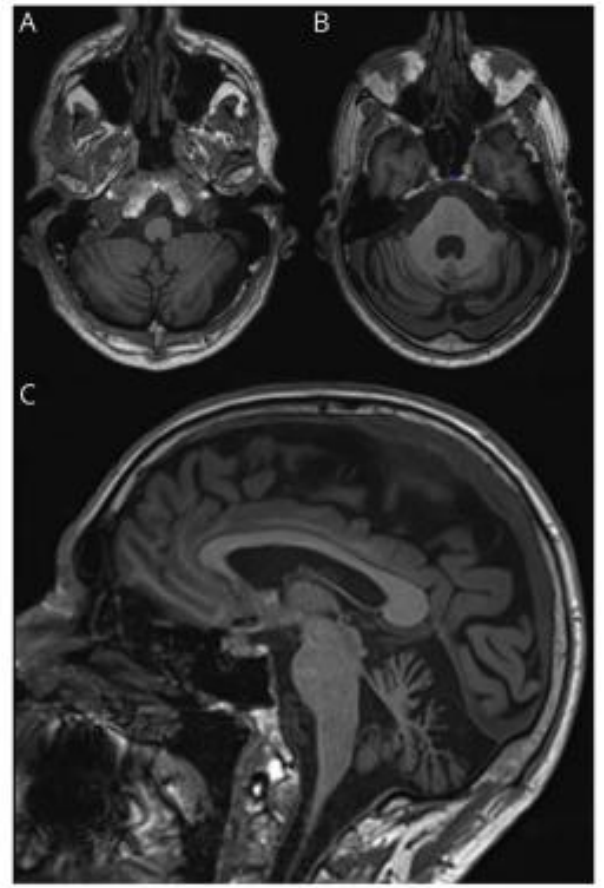
- **Gene Replacement (AAV)**
  - A Study of SGT-212 Gene Therapy in Friedreich's Ataxia (FALCON) (Phase 1b)
- **siRNA**
  - Study of ARO-ATXN2 Injection in Adults With Spinocerebellar Ataxia Type 2 (Phase 1)
- **Antisense oligonucleotide (ASO)**
  - A Phase 1/2a, Open-label Trial to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered VO659 in Participants With Spinocerebellar Ataxia Types 1, 3 and Huntington's Disease (Phase 1,2)
- **Reduction of inflammation and cell death**
  - A Pivotal Study of N-Acetyl-L-Leucine on Ataxia-Telangiectasia (A-T)
- **Protein replacement therapy**
  - An Open-Label Study of CTI-1601 in Subjects With Friedreich's Ataxia (Phase 2)
- **Transcription promotor**
  - A Multiple Ascending Dose Study of DT-216P2 in Patients With Friedreich's Ataxia (Phase 1,2)
- **Reduction of oxidative stress**
  - A Study to Assess the Safety and Efficacy of Vatiquinone in Participants With Friedreich Ataxia (Phase 3)

General Treatments for Cerebellar Ataxia

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Spinocerebellar Ataxia (SCA27B)

- Clinical Presentation
  - Autosomal dominant (variable penetrance)
  - Adult (middle to older)
  - Ataxia
  - Downbeat nystagmus
  - Episodic symptoms



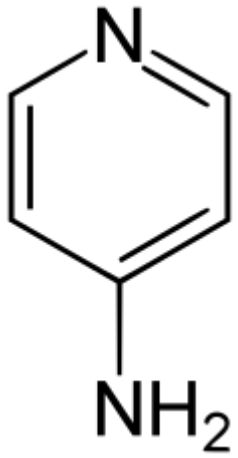
Anderson, etal (2026)



Bill Nye

Dalfampridine (4-AP)

- Mechanism
  - Inhibition of potassium channels (Kv1 Shaker)
    - Prolonged action potentials
  - Potentiate action of voltage gated Ca channels
- Clinical Use
  - Multiple Sclerosis
  - Downbeat nystagmus, especially in SCA27b



Dalfampridine (4-AP), Evidence

- For SCA27b
  - No DB-RCT, but strong clinical evidence from various ataxia centers of excellence
- For DBN
  - Small double blind prospective cross over study- Kalla, etal. (2011)
  - Generally felt to be less effective than in SCA27b

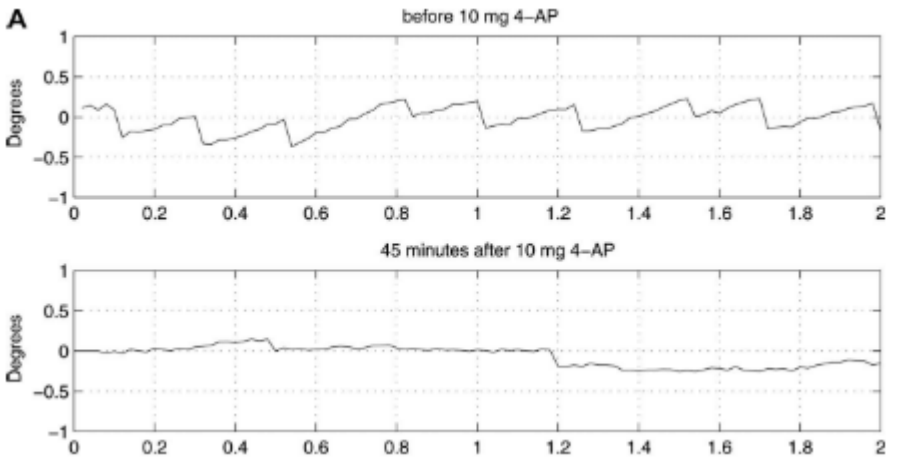
A Randomized, Parallel-arm, Double Blind, Placebo-controlled Study to Assess the Efficacy of Fampridine for Patients With Spinocerebellar Ataxia SCA27B Caused by a GAA Expansion in the FGF14 Gene (TREAT-FGF14)

ClinicalTrials.gov ID NCT07185347

Sponsor Assistance Publique - Hôpitaux de Paris

Information provided by Assistance Publique - Hôpitaux de Paris (Responsible Party)

Last Update Posted 2025-12-10



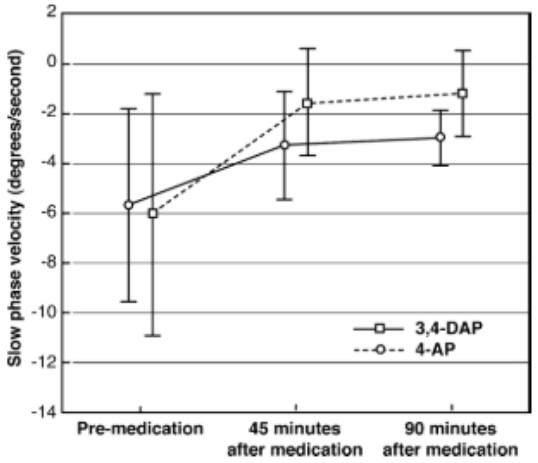


FIG. 2. Comparing mean SPV following treatment with 3,4-DAP and 4-AP prior to medication and 45 minutes and 90 minutes after the administration of medication. Vertical bars denote 95% confidence intervals.

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Physical Therapy



Front Neurol. 2025 Jan 10;15:1491142. doi: 10.3389/fneur.2024.1491142

Effects of physiotherapy on degenerative cerebellar ataxia: a systematic review and meta-analysis

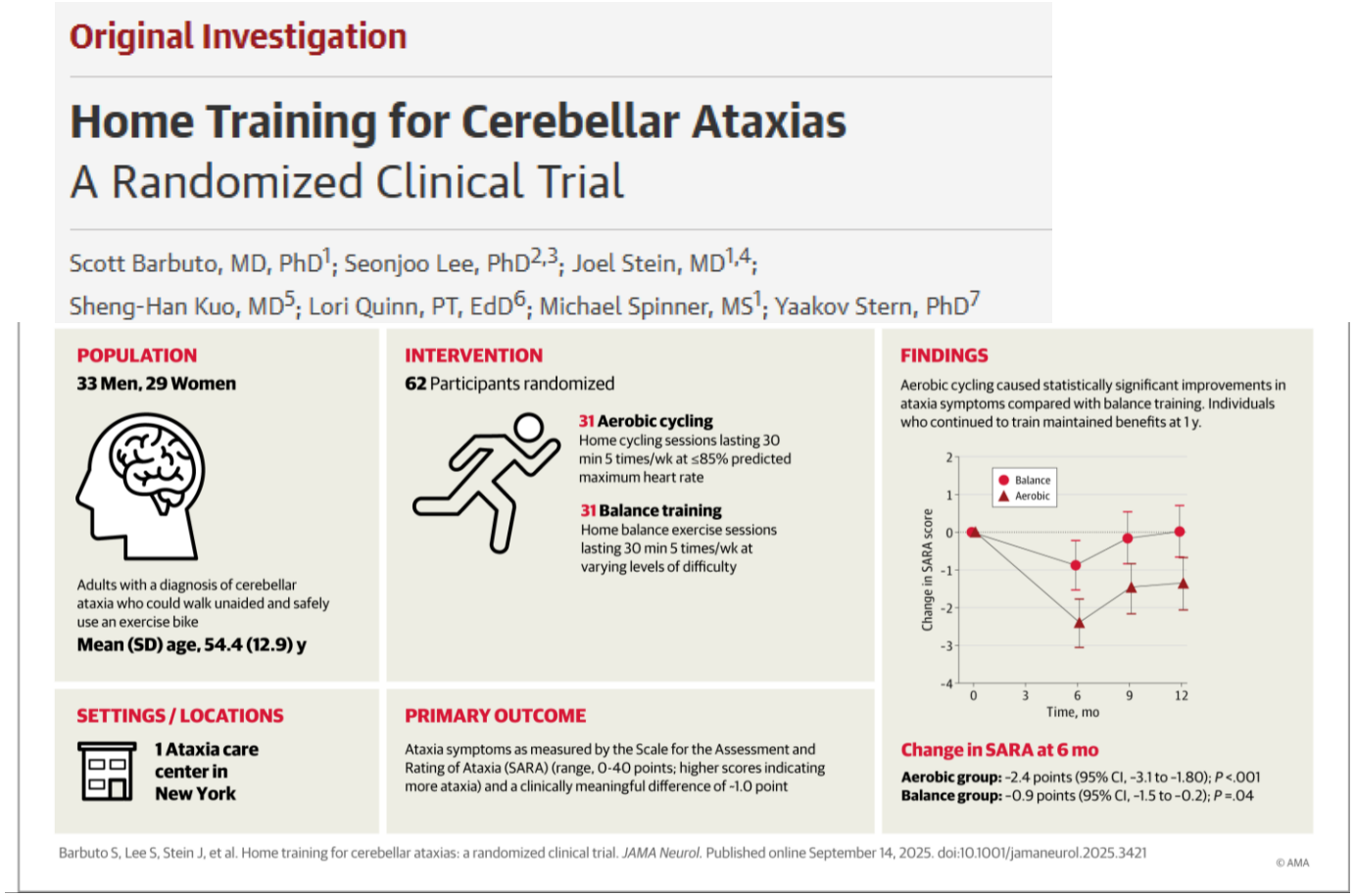
Akiyoshi Matsugi [1,*], Kyota Bando [2], Yuki Kondo [2], Yutaka Kikuchi [3], Kazuhiro Miyata [4], Yuichi Hiramatsu [5], Yuya Yamanaka [6], Hiroaki Tanaka [7], Yuta Okuda [3], Koshiro Haruyama [8], Yuichiro Yamasaki [9]

Author information · Article notes · Copyright and License information

PMCID: PMC11757114 PMID: 39866519

- Results
  - 18 RCTs, 398 participants
  - Significant reduction in SARA scores (-1.41)
  - Multi-aspect, balance, and aerobic beneficial; vibration and dual task training no effect
- Caveat
  - Serious risk of bias, low quality evidence, and heterogeneity

Physical Activity



Original Investigation

Home Training for Cerebellar Ataxias
A Randomized Clinical Trial

Scott Barbuto, MD, PhD[1]; Seonjoo Lee, PhD[2,3]; Joel Stein, MD[1,4]; Sheng-Han Kuo, MD[5]; Lori Quinn, PT, EdD[6]; Michael Spinner, MS[1]; Yaakov Stern, PhD[7]

POPULATION

33 Men, 29 Women

Adults with a diagnosis of cerebellar ataxia who could walk unaided and safely use an exercise bike

Mean (SD) age, 54.4 (12.9) y

INTERVENTION

62 Participants randomized

31 Aerobic cycling
Home cycling sessions lasting 30 min 5 times/wk at ≤85% predicted maximum heart rate

31 Balance training
Home balance exercise sessions lasting 30 min 5 times/wk at varying levels of difficulty

FINDINGS

Aerobic cycling caused statistically significant improvements in ataxia symptoms compared with balance training. Individuals who continued to train maintained benefits at 1 y.

Change in SARA at 6 mo

Aerobic group: −2.4 points (95% CI, −3.1 to −1.80); *P* <.001
Balance group: −0.9 points (95% CI, −1.5 to −0.2); *P* =.04

SETTINGS / LOCATIONS

1 Ataxia care center in New York

PRIMARY OUTCOME

Ataxia symptoms as measured by the Scale for the Assessment and Rating of Ataxia (SARA) (range, 0-40 points; higher scores indicating more ataxia) and a clinically meaningful difference of -1.0 point

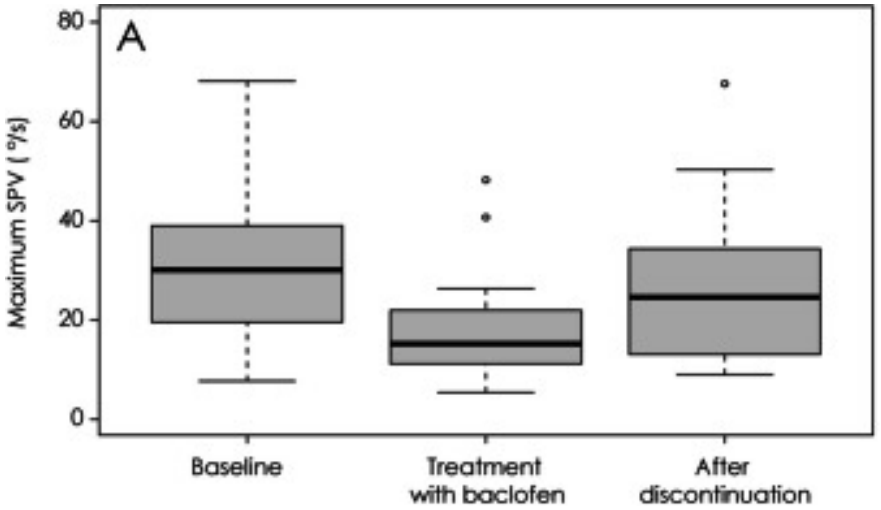
Barbuto S, Lee S, Stein J, et al. Home training for cerebellar ataxias: a randomized clinical trial. *JAMA Neurol.* Published online September 14, 2025. doi:10.1001/jamaneurol.2025.3421

© AMA

- High intensity physical activity improved disease manifestations (SARA score) more than balance training

Muscle Relaxants

- Baclofen
- Chlorzoxazone-baclofen



Effect of Baclofen on DBN (n=15) (Yun et al, 2024)

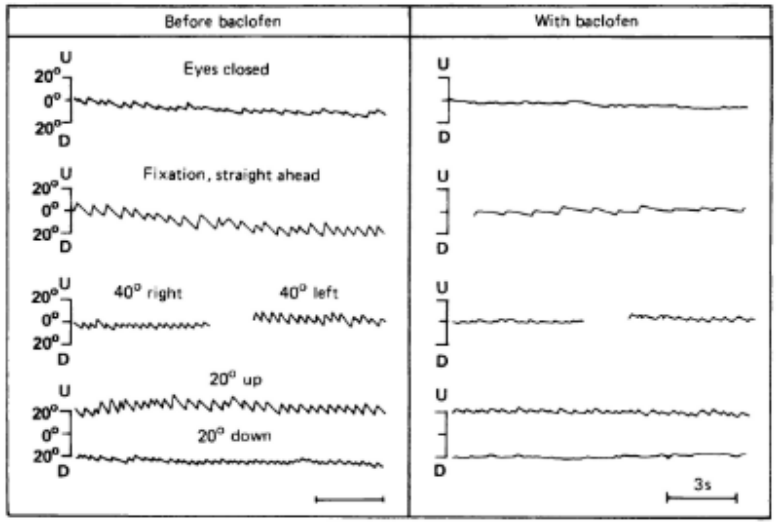


Figure 1 EOG-recordings of vertical eye-movements in a patient (1) with upbeat nystagmus due to a metastasis of the right ponto-medullary brainstem. Considerable suppression of upbeat nystagmus (57% reduction in slow phase velocity) by oral treatment with baclofen, 5 mg three times daily.

Dieterich et al, 1991

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Riluzole/Troriluzole

- Mechanism
  - Riluzole –
    - modulation of glutamate
    - reduction of overactivation of NMDA/AMPA
    - Antioxidant effects
  - Troriluzole – prodrug converted to riluzole
    - Increased bioavailability compared to riluzole

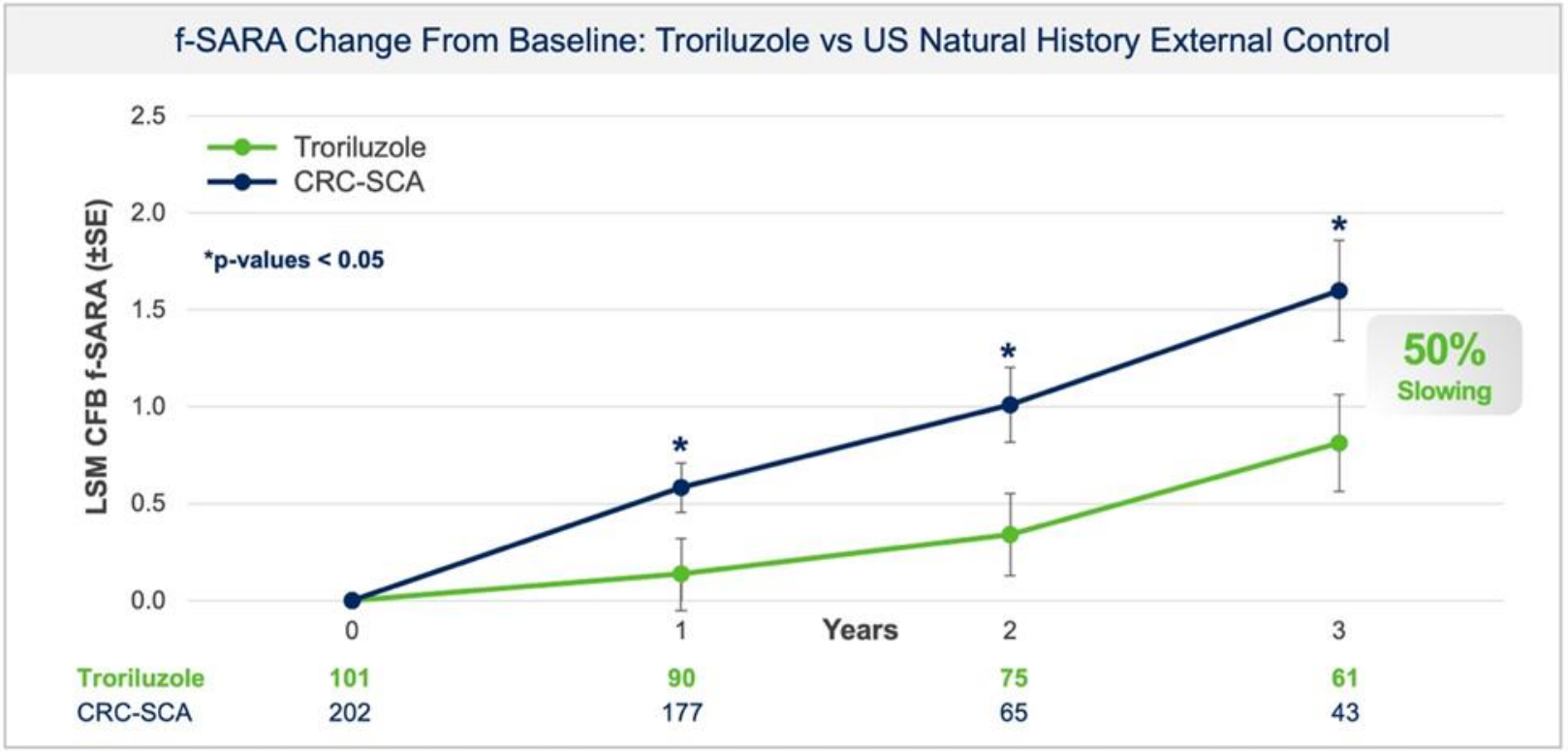
Troriluzole

Arm/Group Title	Troriluzole	Placebo
Arm/Group Description	Randomization phase (Randomization through Week 48): Participants received starting dose of troriluzole 140 milligrams (mg) capsules orally once daily for first 4 weeks, followed by 200 mg once daily for the remaining 44 weeks of 48 week duration of the double-blind randomization phase.	Randomization phase (Randomization through Week 48): Participants received troriluzole matching placebo capsules orally once daily for 48 weeks duration of the double-blind randomization phase.
Overall Number of Participants Analyzed	94	95
All SCA		
Number Analyzed	94 participants	95 participants
*Least Squares Mean (Standard Error) | Unit of Measure: score on a scale	0.20 (0.19)	0.27 (0.18)
SCA3		
Number Analyzed	38 participants	40 participants
*	-0.03 (0.20)	0.53 (0.19)

* Least Squares Mean (Standard Error) | Unit of Measure: score on a scale

Statistical Test of Hypothesis	
P-Value	0.7581
Comments	[Not Specified]
Method	Mixed Models Analysis
Comments	[Not Specified]
Method of Estimation	
Estimation Parameter	Least squares mean difference
Estimated Value	-0.06
Confidence Interval	(2-Sided) 95% -0.47 to 0.34
Parameter Dispersion	Type: Standard Error of the Mean Value: 0.20

Troriluzole



CRC-SCA, Clinical Research Consortium for SCA; **EUROSCA**, European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM**, least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

Potential Future Treatments

Non-invasive and Invasive Neuromodulation

- Examples
  - Transcranial Magnetic Stimulation (TMS)
  - Direct Current Stimulation (tDCS)
  - Spinal Cord Stimulation (SCS)
  - Transcutaneous Peripheral Stimulation
  - Deep Brain Stimulation (DBS)

Effects of Non-Invasive Brain Stimulation for Degenerative Cerebellar Ataxia: A Systematic Review and Meta-Analysis

Akiyoshi Matsugi PT, PhD, Hiroyuki Ohtsuka PT, PhD, Kyota Bando PT, PhD, Yuki Kondo PT, PhD, Yutaka Kikuchi PT, MS

First published: 02 September 2024 | https://doi.org/10.1002/mdc3.14205 | VIEW METRICS

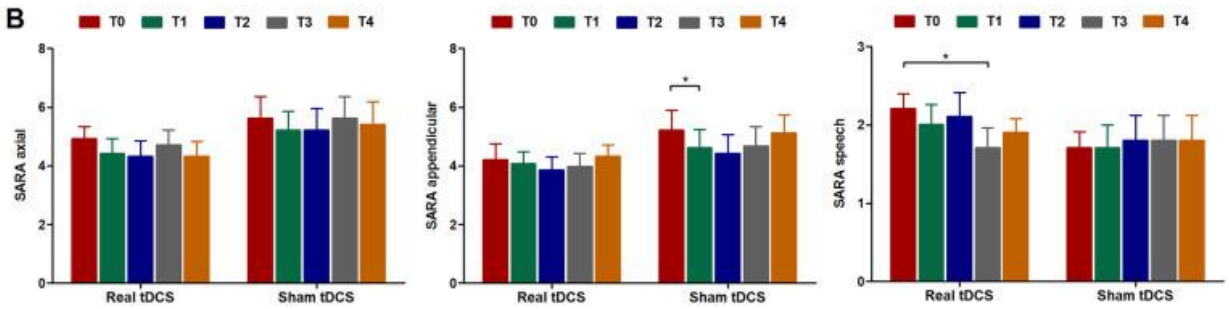
- Aim
  - Evaluate effectiveness of rTMS and transcranial electrical stimulation for degenerative cerebellar ataxia
- Results
  - 17 RCTs, 661 pts
  - Non-invasive stimulation may reduce ataxia
  - Serious risk of bias, low certainty of evidence

ORIGINAL ARTICLE · Volume 19, Issue 4, P1259-1272, July 2022 · Open Access Download Full Issue

Cerebellar Transcranial Direct Current Stimulation in Spinocerebellar Ataxia Type 3: a Randomized, Double-Blind, Sham-Controlled Trial

Roderick P.P.W.M. Maas [1] · Steven Teerenstra [2] · Ivan Toni [3] · Thomas Klockgether [4,5] · Dennis J.L.G. Schutter [6] · Bart P.C. van de Warrenburg [1]

- Methods
  - SCA3 (10 sham, 10 stim)
  - Two-weeks of stim or sham (daily on weekdays)
  - Evaluation at 2w, 3m, 6m, and 12m
  - Primary endpoint = SARA at 2w



- Results
  - Negative
  - Similar lack of efficacy on secondary measures

UT Southwestern Medical Center

Current Trials of Non-Invasive Neuromodulation

Effects of Cerebellar tACS-iTBS in Ataxia (EtABeta)

ClinicalTrials.gov ID NCT06420271

Sponsor I.R.C.C.S. Fondazione Santa Lucia

Information provided by I.R.C.C.S. Fondazione Santa Lucia (Responsible Party)

Last Update Posted 2026-02-17

Current Trials on DBS

Cerebellar Deep Brain Stimulation for the Treatment of Ataxia (DBS-Ataxia)

ClinicalTrials.gov ID NCT07427563

Sponsor University Health Network, Toronto

Information provided by Suneil Kalia, University Health Network, Toronto (Responsible Party)

Last Update Posted 2026-02-23

Interposed Nucleus aDBS for Ataxia

ClinicalTrials.gov ID NCT07325487

Sponsor University of Florida

Information provided by University of Florida (Responsible Party)

Last Update Posted 2026-07-20

Deep Brain Stimulation for Spinocerebellar Ataxia

ClinicalTrials.gov ID NCT07288437

Sponsor University of California, San Francisco

Information provided by Marta San Luciano Palenzuela, MD, University of California, San Francisco (Responsible Party)

Last Update Posted 2026-07-13

Conclusion

- Disease modifying treatments of cerebellar ataxia exist and evaluation for disorders that can be modified should be performed
- Cerebellar ataxias are always treatable and regular neurological care is important
- The future is bright and there are many potential treatments in the pipeline