Medications and Diet for Ataxia

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DISCLAIMER

2025 Annual Ataxia Conference
March 29-30, 2025
Planet Hollywood
Las Vegas, NV

NAF National Ataxia Foundation

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PRESENTER DISCLOSURES

Dr. Susan L. Perlman

The following personal financial relationships with commercial interests' relevant to this presentation existed during the past 12 months:

Member of Advisory Board or Consultant for Biogen, Biohaven, Erydel, PTC, Reata, Samsara, Seelos, Steminent.

NAF National Ataxia Foundation

What you don’t want to hear from your doctor

- You have ataxia and there’s nothing I can do.
- I don’t know what you have and there’s nothing I can do.

- Patients need to play an active role in educating their doctors and keeping communication open.
- Don’t be afraid to bring up things you have seen on various websites or heard from other patients and practitioners.
- Be sure your doctors know what you are doing outside of what they have prescribed.

Things your doctor can and should do

- Confirm that the gait abnormality is cerebellar ataxia or at least has a cerebellar component (other factors could be double vision, dizziness, rigidity, spasticity, weakness, sensory loss, arthritis)
- Confirm a genetic or non-genetic/acquired cause of the ataxia syndrome
- Clarify the risks for other family members
- Assess the patient's psychosocial, support, and disability needs
- Help patient connect to clinical research and clinical trials
- Rehabilitation interventions always help (home exercise, assistive devices, fall prevention)
- Symptomatic medications can improve quality of life
- Disease-modifying treatments are in the pipeline
- Most ataxia specialists are willing to consult or at least provide advice

Treatable Cerebellar Ataxias

Acquired ataxias: the clinical spectrum, diagnosis and management.

Nachbauer W, Eigentler A, Boesch S.J Neurol. 2015 May;262(5):1385-93.

Autoimmune ataxias

Laboratory investigations: onconeural antibodies (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma2, anti-CV2), cell surface antibodies (anti-mGluR1, anti-VGCC), anti-GAD, thyroid status, anti-TPO, gliadin and transglutaminase antibodies

Paraneoplastic disorders

Antibodies to intracellular antigens (onconeural)

Antibodies to cell surface antigens

Non-paraneoplastic disorders

Anti-GAD ataxia

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)

Gluten ataxia

Cont'd

Toxic cerebellar degeneration

Laboratory investigations: liver function, ammonia levels, screening for drugs and toxins, serum vitamin B1 levels

Alcoholic cerebellar degeneration (ACD)

Medicines/drugs

Chemical toxins

Thermic cerebellar degeneration

Metabolic disorders

Vitamin deficiency disorders

Laboratory investigations: serum vitamin B and E levels, methylmalonic acid, total homocysteine

Vitamin B1 deficiency/Wernicke's encephalopathy (WE)

Vitamin B12 deficiency

Vitamin E deficiency

Infectious cerebellar diseases

Laboratory investigations: serologic testing in CSF

Acute cerebellitis

Acute post/para-infectious cerebellar ataxia

Chronic CNS infections

Treatable Cerebellar Ataxias cont'd

Guidelines on the diagnosis and management of the progressive ataxias.

de Silva R, Greenfield J, Cook A, Bonney H, Vallortigara J, Hunt B, Giunti P.Orphanet J Rare Dis. 2019 Feb 20;14(1):51.

Predominantly the inborn errors of metabolism which can present in adulthood

Gluten ataxia

Vitamin E deficiency, Vitamin B12 deficiency, CoQ10 deficiency

CTX, NPC

Table 5 Treatable ataxias

5.1 Gluten ataxia

Recommendation

It is recommended that patients with idiopathic cerebellar ataxia are tested for gluten sensitivity.

Consider testing for antibodies against TG6 (when possible) as a more sensitive test for gluten ataxia.

Ataxia patients with or without enteropathy who have serological evidence of gluten sensitivity should be advised to start a gluten-free diet without delay.

Patients who are starting a gluten-free diet should be advised about strict adherence and given dietetic advice.

Close monitoring is recommended with six-monthly testing to ensure for elimination of antigliadin antibodies.

5.2 Ataxia with vitamin E deficiency

Recommendation

Patients diagnosed with ataxia with vitamin E deficiency or abetalipoproteinemia should be treated with vitamin E supplements.

5.3 Ataxia with vitamin B12 deficiency

Recommendation

Patients diagnosed with ataxia and Vitamin B12 deficiency should be treated with Vitamin B12.

5.4 Ataxia with CoQ10 (ubiquinone) deficiency

Recommendation

Patients diagnosed with ataxia with CoQ10 deficiency should be treated with CoQ10 supplements.

Consider treatment of patients diagnosed with AOA1 with CoQ10 supplementation.

5.5 Cerebrotendinous xanthomatosis

Recommendation

Prompt diagnosis of cerebrotendinous xanthomatosis is advised in order to initiate treatment.

If cerebrotendinous xanthomatosis is diagnosed treatment with chenodeoxycholic acid is recommended.

5.6 Niemann-Pick type C (NPC)

Recommendation

If NPC is suspected based on clinical investigations, perform diagnostic tests described above. Early diagnosis is important as it is a treatable condition.

If NPC is diagnosed refer promptly to a Specialist Centre for treatment and management.

Treatment with Miglustat is recommended in both adult and paediatric cases and is available in Specialist Centres.

Abstracts from the AAN 2025 meeting in San Diego April 5-9
136 dealt with ataxia

- Somatic expansion in SCA27b
- 5 other for SCA27b
- 2 for CANVAS
- 9 looking at other SCAs; 4 at treatments
- 50 looking at other genetic and acquired ataxias; 3 at treatments
- 43 looking at autoimmune ataxias; 1 at treatments
- 2 at MSA; 1 at treatment
- 15 others with something to do with ataxia

There are two FDA approved therapies for two of the common genetic ataxias—

Skyclarys (omaveloxolone) for Friedreichs ataxia.
https://www.skyclarys.com/

Aqneursa (levacetylleucine) for Niemann-Pick type C.
https://www.aqneursa.com/

There are as yet no other FDA-approved drugs for the treatment of any other type of inherited ataxia.

Troriluzole for SCA and Vatiquinone (PTC743) are with the FDA now.

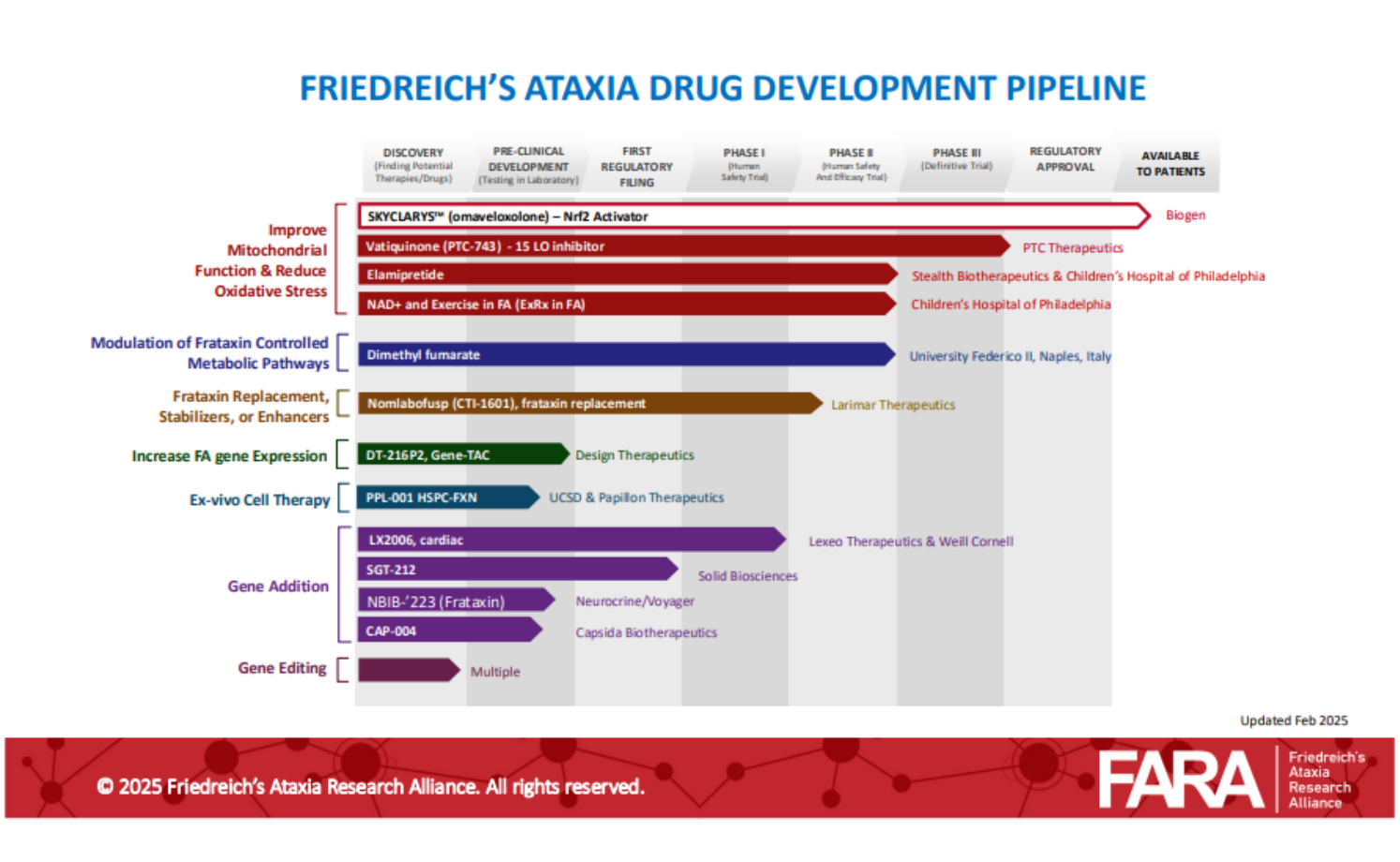
Troriluzole is currently in an Expanded Access Program for any SCA.

The Road to FDA Approval

- Candidate drugs with preclinical activity and safety data.
- Big Pharma willing to take on human trials.
- Rating scales—SARA, f-SARA, FARS, mFARS, FARS ADL, ICARS, mICARS.
- Natural history databases for propensity matched analysis—

  CRC-SCA NHS, EuroSCA, FACOMS/EFACTS/UNIFAI, others in development for LOTS, A-T, MSA
- Proper trial design—I/E criteria, how many patients in each arm, how long to run the trial.
- Recruitment.

Friedreich's Ataxia Pipeline
https://www.curefa.org/pipeline



SkyClarys (Omaveloxolone) for Friedreichs Ataxia

www.Skyclarys.com

Includes links for health care providers and patients.

Includes links to the Biogen REACH program for information about Prescribing, Insurance and copay, Copay assistance, and At-home prescription delivery from the Specialty Pharmacy (Biologics).

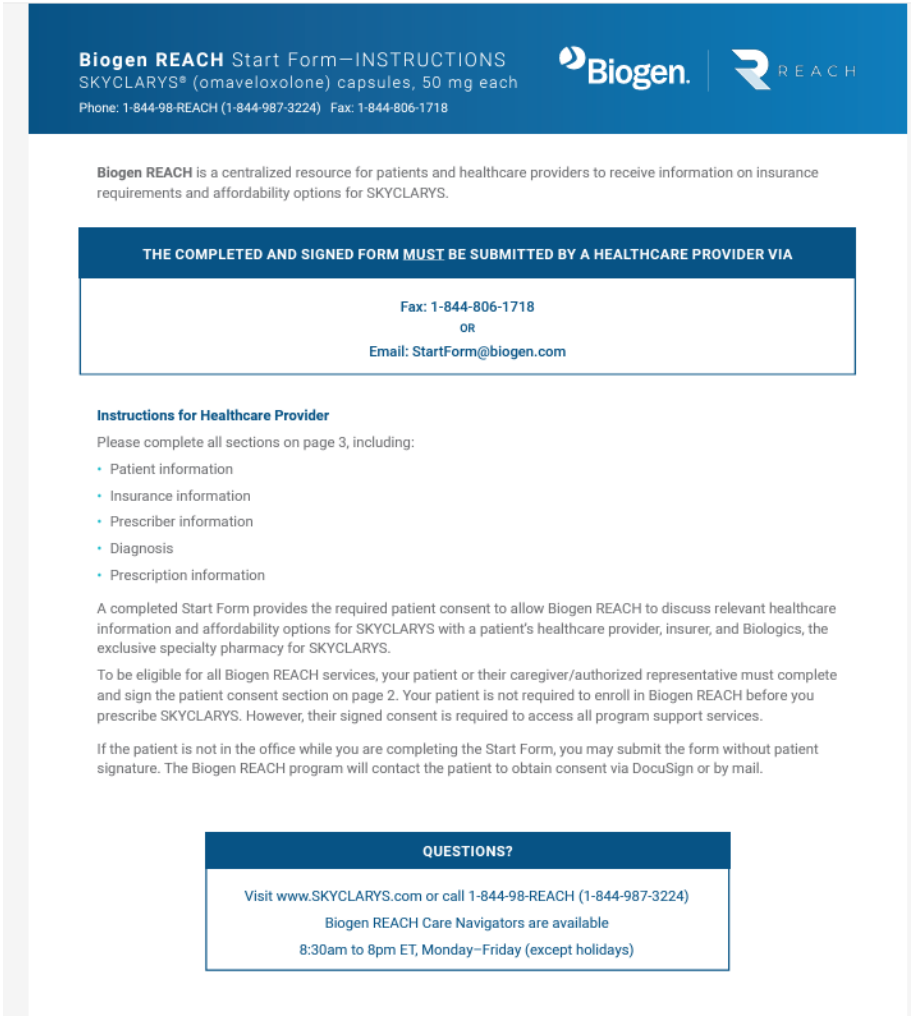
SKYCLARYS is indicated for the treatment of FA in patients aged 16 years and older

- No contraindications or limitations based on pes cavus, cardiovascular status, ambulation, mFARS score, or older age
- **Planning to engage with the FDA about possible label expansion for pediatric patients younger than 16 years of age**

In addition to the post-marketing requirements, Reata will sponsor a post-marketing registry study

- Prospective, observational, multinational study
- Patients with FA treated with SKYCLARYS commercially

Objective is to evaluate long-term safety in the real world setting



Biogen REACH Start Form—INSTRUCTIONS
SKYCLARYS® (omaveloxolone) capsules, 50 mg each
Phone: 1-844-98-REACH (1-844-987-3224) Fax: 1-844-806-1718

Biogen REACH

Biogen REACH is a centralized resource for patients and healthcare providers to receive information on insurance requirements and affordability options for SKYCLARYS.

THE COMPLETED AND SIGNED FORM MUST BE SUBMITTED BY A HEALTHCARE PROVIDER VIA

Fax: 1-844-806-1718
OR
Email: StartForm@biogen.com

Instructions for Healthcare Provider

Please complete all sections on page 3, including:

- Patient information
- Insurance information
- Prescriber information
- Diagnosis
- Prescription information

A completed Start Form provides the required patient consent to allow Biogen REACH to discuss relevant healthcare information and affordability options for SKYCLARYS with a patient's healthcare provider, insurer, and Biologics, the exclusive specialty pharmacy for SKYCLARYS.

To be eligible for all Biogen REACH services, your patient or their caregiver/authorized representative must complete and sign the patient consent section on page 2. Your patient is not required to enroll in Biogen REACH before you prescribe SKYCLARYS. However, their signed consent is required to access all program support services.

If the patient is not in the office while you are completing the Start Form, you may submit the form without patient signature. The Biogen REACH program will contact the patient to obtain consent via DocuSign or by mail.

QUESTIONS?

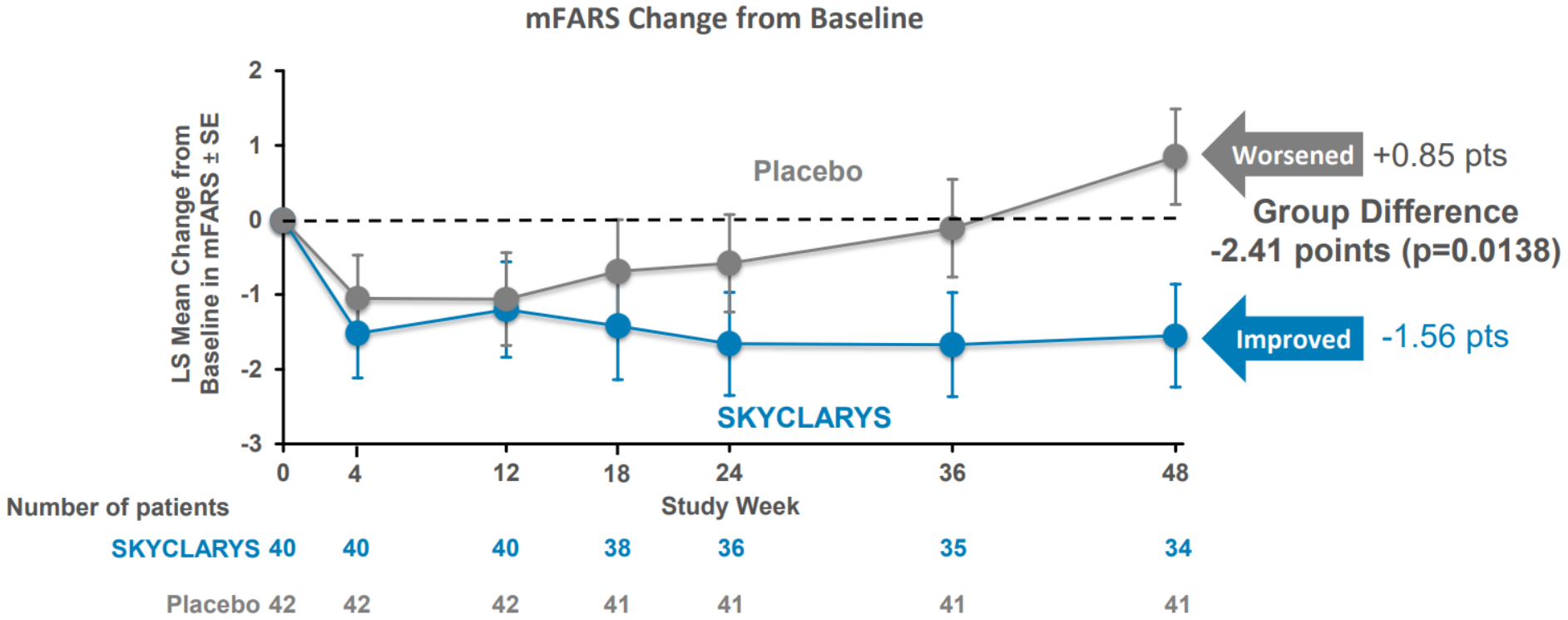
Visit www.SKYCLARYS.com or call 1-844-98-REACH (1-844-987-3224)
Biogen REACH Care Navigators are available
8:30am to 8pm ET, Monday–Friday (except holidays)

Overview of Prescribing Information

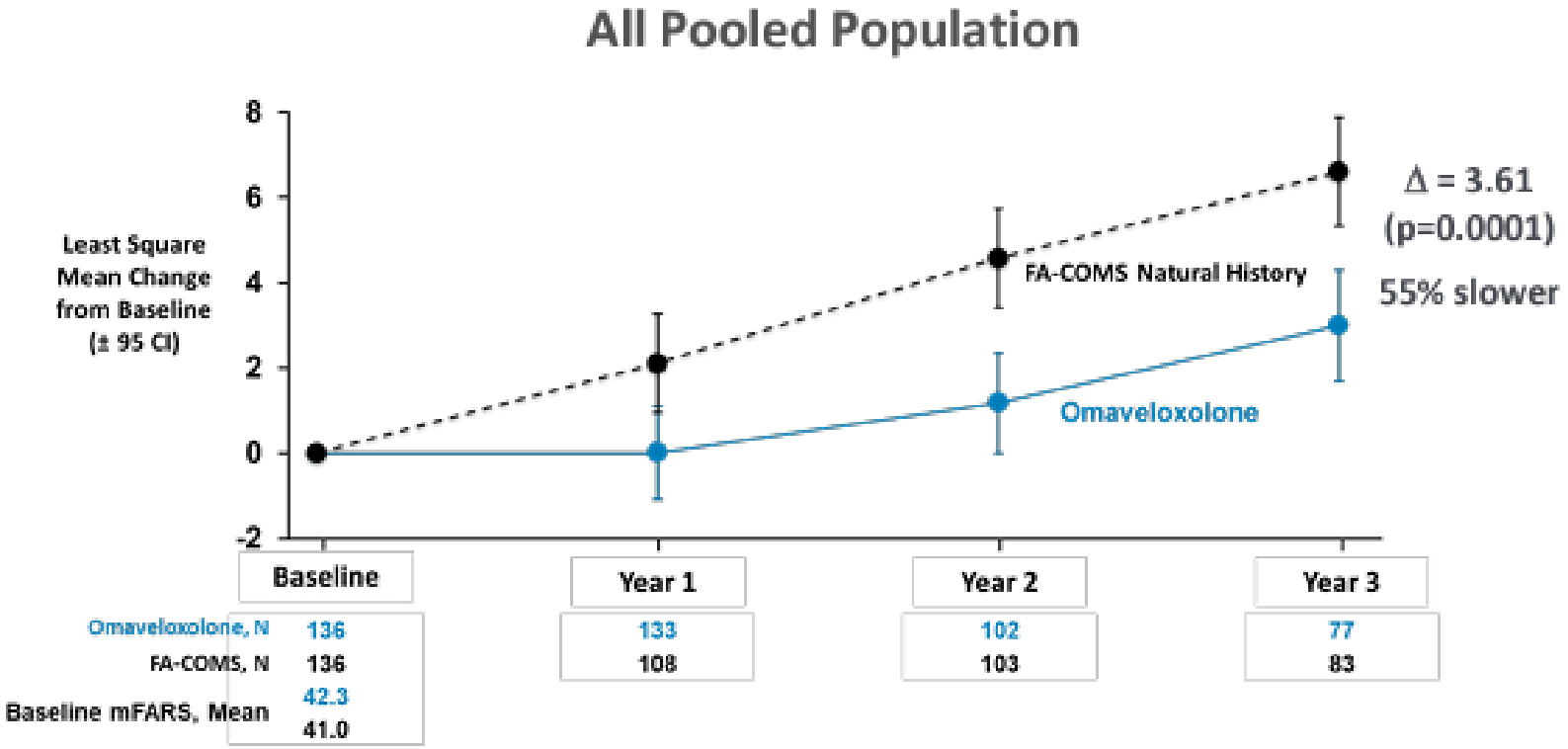
- Contraindications None
- Boxed Warning None
- Risk Evaluation and Mitigation Strategy None
- Dosing and Administration--Obtain ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating SKYCLARYS and monthly for first 3 months during treatment.
- Recommended dosage of SKYCLARYS is 150 mg (3 capsules) taken orally once daily. Dose can be lowered depending on side effects.
- Warnings and Precautions--Elevation of Aminotransferases; Elevation of B-type Natriuretic Peptide (BNP); Lipid Abnormalities
- Adverse Reactions--Most common adverse reactions (incidence ≥20% and greater than placebo) are elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.
- Most side effects resolve on their own after about a month.

MOXIe Part 2 Placebo-Controlled Trial Results

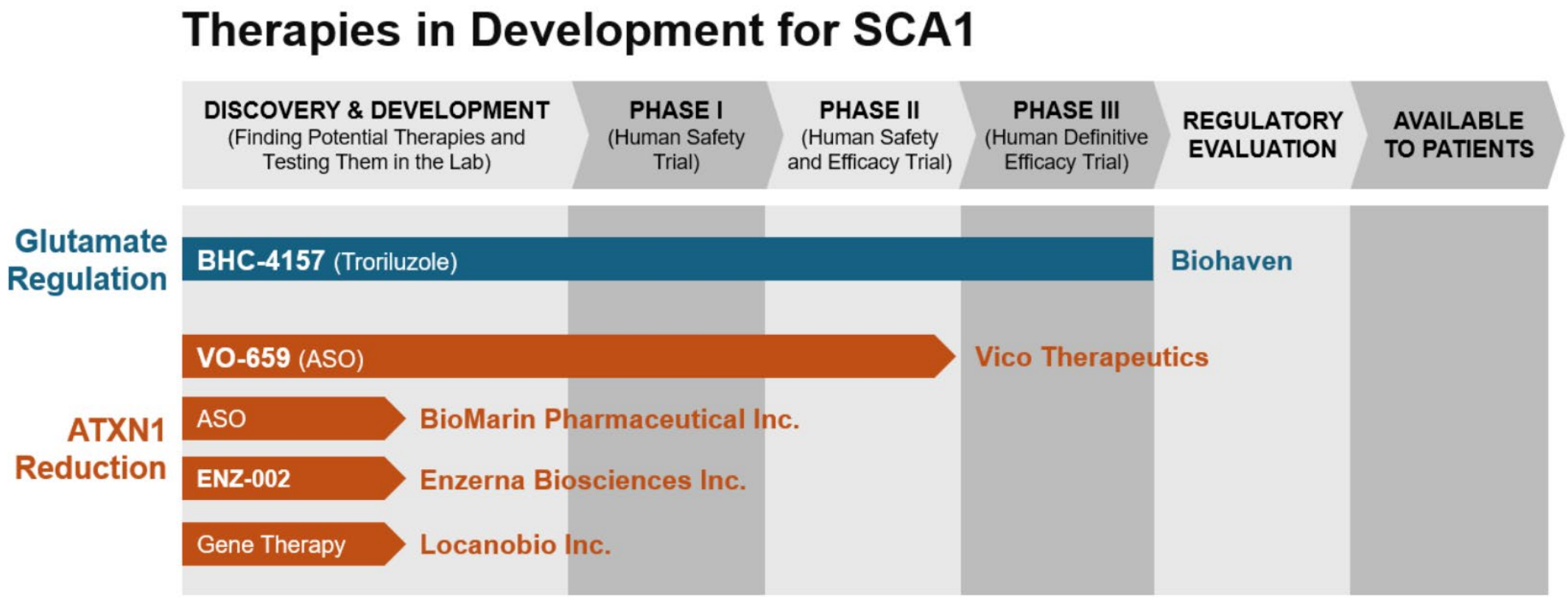
Treatment with SKYCLARYS resulted in statistically significant lower (improved) mFARS scores relative to placebo at Week 48



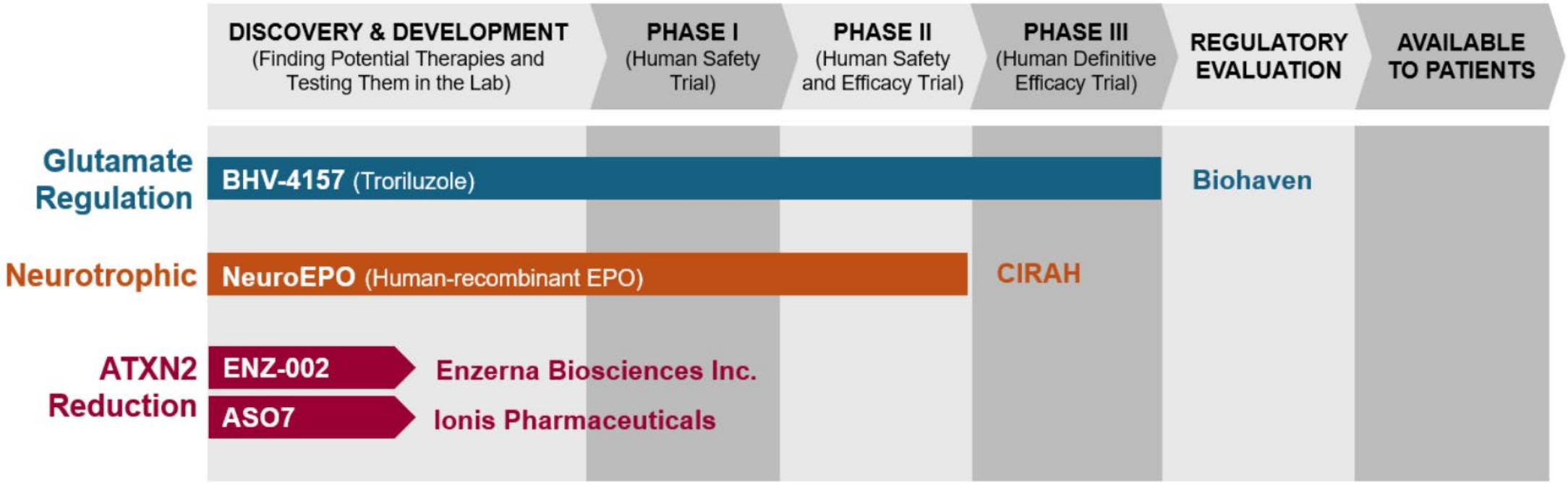
Propensity-Matched Analysis: Use of External Natural History Control Group



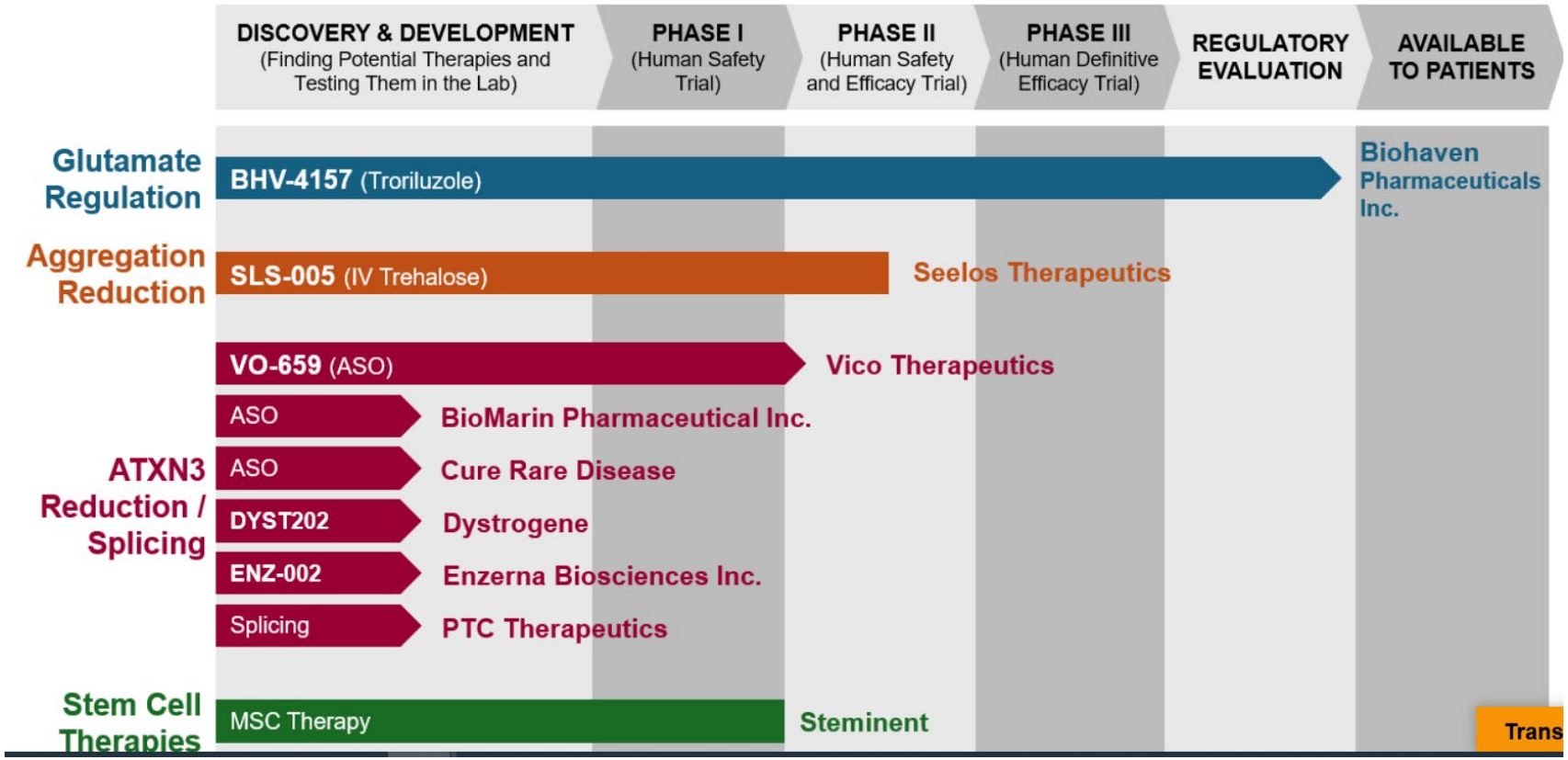
Spinocerebellar Ataxia Pipelines
(from the National Ataxia Foundation Website)



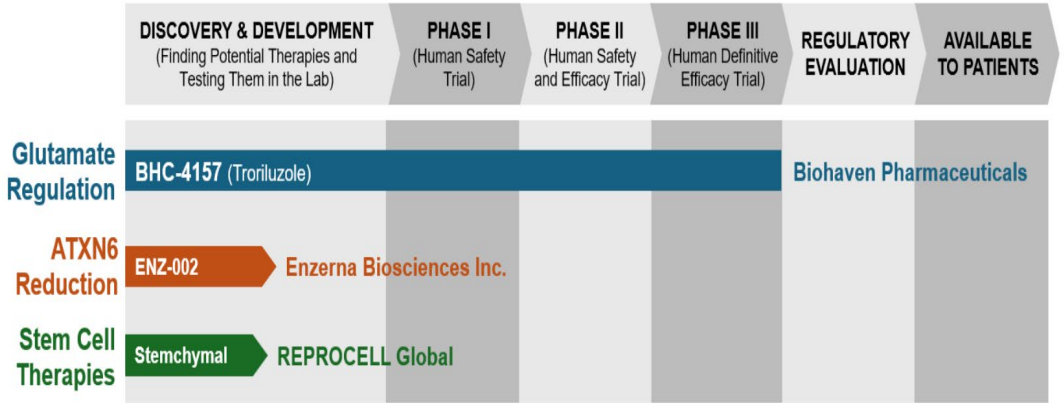
Therapies in Development for SCA2



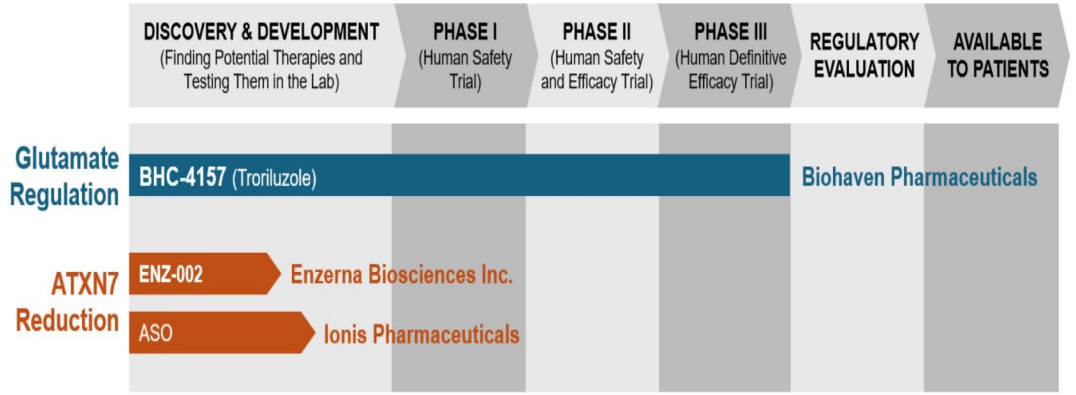
Therapies in Development for SCA3



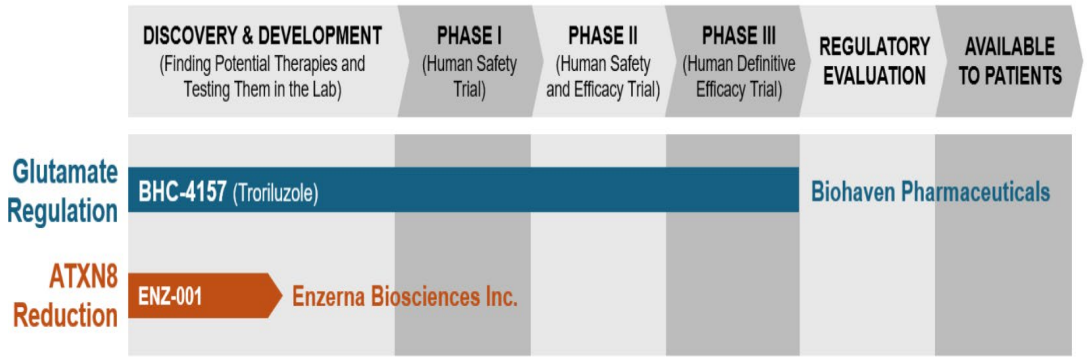
Therapies in Development for SCA6



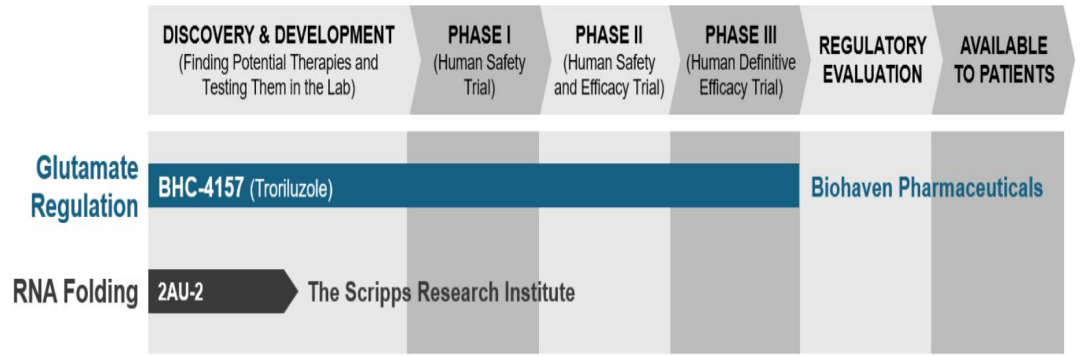
Therapies in Development for SCA7



Therapies in Development for SCA8



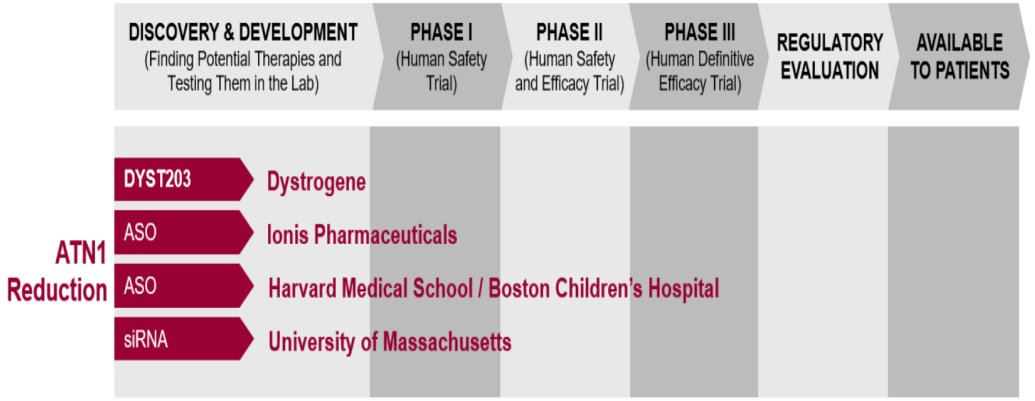
Therapies in Development for SCA10



To learn more about ongoing DRPLA research, please visit CureDRPLA.

Therapies in Development for SCA17

Therapies in Development for DRPLA



Who is Enzerna?

- Enzerna Biosciences, Inc is a pre-clinical stage company that is leveraging its proprietary RNA editing technology to develop long-term curative gene therapies for rare genetic disorders.
- Our therapeutic platform, called Artificial Site Specific RNA Endonucleases (ASREs) is modular system consisting of an RNA binding module (PUF) that can be engineered to bind any RNA sequence of choice and an RNA degrading enzyme (PIN) that will destroy the RNA. ASREs can be used to specifically cleave (and thus inactivate) any disease-causing RNA. Combined with gene delivery vectors, ASREs provide a new strategy for selective degradation of pathogenic transcripts associated with nucleotide expansion disorders.
- Antisense oligonucleotide (ASO) and RNA interference (RNAi)- based therapies have been shown to be effective in isolated cells. However, these therapies are limited by the need for lifelong administration, poor delivery across the blood brain barrier, and passive delivery to target cells in vivo. While antisense RNAs could be delivered via gene therapy, to date, targeting efficiency remains unacceptably low.
- For many diseases, gene editing, most notable using CRISPR/Cas DNA editing technology, offers an opportunity to correct mutant alleles. Unfortunately, given the mechanism of the gene editing process, CRISPR/Cas currently does not offer a viable therapeutic approach for nucleotide expansion disorders.
- ASRE's Have the Following Competitive Advantages:
- **Human-based**
- **Non CRISPR-based**
- **No competing Intellectual Property**
- **ASREs preferentially bind and destroy RNAs carrying expanded repeats leaving normal RNAs intact (cf. WaveLife Science's SNP allele-specific ASOs for Huntington's Disease)**
- **One ASRE therapeutic can be used to treat multiple indications**

- Enzerna has secured an exclusive license for ASRE technology (US Patent No. 9,499,805) from the University of North Carolina-Chapel Hill for all commercial applications.

- **6 ongoing trials for Ataxia Telangiectasia**
- **A-T Childrens Project https://atcp.org/**

NEAT
This trial will evaluate the effects of EryDex in patients with A-T. ›

Global A-T Family Data Platform
The Platform is a patient-driven effort through which data about people with A-T are shared with researchers. ›

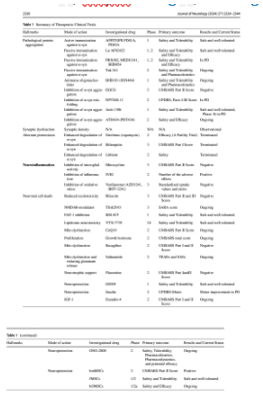
Pulmonary Function Study
This study seeks to establish the natural history of pulmonary function decline in the A-T population. ›

Swallowing Study
Goals of this study are to develop non-invasive markers that will lessen the impact of swallowing dysfunction. ›

IB1001 TRIAL
IntraBio, Inc. is studying the effects of N-Acetyl-L-Leucine on A-T. ›

Machine Vision and Learning for A-T Neurophenotypes
This study seeks to develop sensitive, automated and objective means of measuring neurological disease severity. ›

- **Since 2013, Mission MSA (formerly The MSA Coalition) has funded 75 MSA-focused research projects for Multiple System Atrophy (pathogenesis, diagnostic biomarkers, preclinical, clinical). No longer posts a pipeline.**
- **But**
- J Neurol. 2024 May;271(5):2324-2344
- **Multiple system atrophy: an update and emerging directions of biomarkers and clinical trials** Min Liu , Zhiyao Wang , Huifang Shang
- Profiles trials targeting alpha synuclein, synaptic dysfunction, neuroinflammation, cell death, and neuroprotection.



MSA DMD Trials currently active in the US

Trial name	Lundbeck Phase 2	Lundbeck Phase 3	Takeda Phase 2	Teva Phase 2	Alterity Phase 2	ONO Phase 2	Yoda Phase 2
MOA	**Lu AF82422** **Amethyst** Humanized monoclonal IgG1 antibody targeting the C-terminal of α-synuclein. In the subgroup analysis by MSA type, a substantial signal of efficacy was seen across UMSARS and subdomains in participants with MSA-C, with a slowing of clinical progression >50% (UMSARS TS and mUMSARS and UMSARS Part I scores). **Monthly IV x 1yr**	**Lu AF82422** **MASCOT** Recombinant anti-alpha-synuclein human IgG1 monoclonal antibody This is a Phase III, interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled, optional open-label extension trial with the aim to evaluate the efficacy, safety, and tolerability of Lu AF82422 in participants with MSA. **72-week double-blind PCP 1:1:1 and an optional dose-blinded OLE period**	**TAK-341** High-affinity monoclonal antibody to a C-terminal epitope on monomeric and aggregated α-synuclein Multiple protocol revisions and delays. **Monthly IV x 1yr**	**TEV-56286** **MODAG** **TOPAS-MSA** Anle138b is an oral, brain-penetrant, general inhibitor of protein aggregation. It was identified in a high-throughput screen for small-molecule inhibitors of α-synuclein and prion protein oligomerization **Oral x 1y 1:1**	**ATH434** Inhibition of iron-mediated protein aggregation via reduction of the labile iron pool; reduced oligomeric and urea soluble α-synuclein aggregation, reduced the number of GCIs, and preserved SNpc neurons. Anti-ox, mitoch protectant **Oral x 1yr 1:1:1**	**ONO-2808** Small molecule sphingosine-1-phosphate receptor-5 (S1PR5) agonist promotes remyelination and reduces pathogenic CNS α-synuclein accumulation. **Oral x 6mo with OLE 3:1**	**YA-101** Modulation of NMDAR and the NLR family pyrin domain containing 3 (NLRP3) inflammasome has been suggested as potential therapeutic targets for MSA. YA-101 (RS-D7) is a New Chemical Entity (NCE) specifically designed to treat MSA as a potent D-amino acid oxidase (DAAO) inhibitor and NLRP3 modulator. 28-day treatment, 28-day follow-up, multiple ascending dose, proof of concept study to assess the safety, tolerability, pharmacokinetics and efficacy of YA-101 in multiple system atrophy **Oral—2 cohorts after one month starter cohort-- 1:1:1 x 12 weeks**
Age	40-75	40-75	40 or older	>30	30-75	30-80	30
Years of sxx	< or = 5y	< or = 5y	< or = 4y	< or = 5y	< or = 4y	< or = 5y	No limit

Dx criteria	Possible or Probable	Clinically established or probable	Possible or Probable	Possible or Probable	Probable	Possible or Probable	Clinically established or probable
Exam criteria	UMSARS 1 <16 MOCA >22	English speaking. Caregiver MRI, LP UMSARS 1 <16 MOCA >22 Walker allowed	Ambulatory <50% with assistance	Ambulatory 10m with non human assist allowed—only SPC	All three areas involved Ambulatory	English speaking. Caregiver Perfect liver UMARS 1 <17 Ambulatory Walker allowed	MRI, EEG, LP, gait video Cane or walker or person
							No stem cell trials
	Closed to enrollment Phase 3 planned	To enroll 360 in Europe, North America, Asia	Closed to enrollment—136 in Europe, North America, Asia	Opening for recruitment in September 2024	Closed to enrollment with 77 at 23 locations at Columbia, Vanderbilt, Italy, UK, Australia, NZ	To enroll at least 80 at 36 sites.	To enroll 8+60 at 10 centers in 2 countries (Taiwan and United States)

- MSA trials failed at UCLA—Rifampicin, Open Biohaven, Verdiperstat
- Not moving forward—Servier Ph1b MAD study as well as the Disruptive clinical trial
- 6 studies recruiting for neurogenic orthostatic hypotension

- Despite efforts over the past decade, potential therapies targeting α-synuclein pathology, such as rapamycin, riluzole, minocycline, lithium, and nilotinib, have failed in animal models and clinical trials. Research has also indicated that α-synuclein aggregates can cause NMDA receptor (NMDAR) hypofunction and increased microglial activation. Modulation of NMDAR and the NLR family pyrin domain containing 3 (NLRP3) inflammasome has been suggested as potential therapeutic targets for MSA.

There is one approved drug in Japan for ataxia

- **Taltirelin** (marketed under the tradename **Ceredist**) is a thyrotropin-releasing hormone (TRH) analog, which mimics the physiological actions of TRH, but with a much longer half-life and duration of effects, and little development of tolerance following prolonged dosing. It has nootropic, neuroprotective, and analgesic effects.
- It has been available in Japan for over 15 years (Mitsubishi Tanabe Pharma. October 2007).
- It can be obtained in Japan from a licensed physician and in amounts sufficient to last from one visit to the next.

There are two drugs recognized by the AAN as appropriate for off-label use for ataxia

- **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.Zesiewicz TA, Wilmot G, Kuo SH, Perlman S, Greenstein PE, Ying SH, Ashizawa T, Subramony SH, Schmahmann JD, Figueroa KP, Mizusawa H, Schöls L, Shaw JD, Dubinsky RM, Armstrong MJ, Gronseth GS, Sullivan KL.Neurology. 2018 Mar 6;90(10):464-471. WILL BE UPDATED SOON**
- For patients with episodic ataxia type 2, 4-aminopyridine 15 mg/d probably reduces ataxia attack frequency over 3 months (1 Class I study).
- For patients with ataxia of mixed etiology, riluzole probably improves ataxia signs at 8 weeks (1 Class I study). For patients with Friedreich ataxia or spinocerebellar ataxia (SCA), riluzole probably improves ataxia signs at 12 months (1 Class I study).

- For patients with SCA type 3, **valproic acid** 1,200 mg/d possibly improves ataxia at 12 weeks.
- For patients with spinocerebellar degeneration**, thyrotropin-releasing hormone** possibly improves some ataxia signs over 10 to 14 days (1 Class II study).
- For patients with SCA type 3 who are ambulatory, **lithium** probably does not improve signs of ataxia over 48 weeks (1 Class I study).
- For patients with Friedreich ataxia, **deferiprone** possibly worsens ataxia signs over 6 months (1 Class II study). Data are insufficient to support or refute the use of numerous agents.
- For nonpharmacologic options, in patients with degenerative ataxias, **4-week inpatient rehabilitation** probably improves ataxia and function (1 Class I study); **transcranial magnetic stimulation** possibly improves cerebellar motor signs at 21 days (1 Class II study). For patients with multiple sclerosis–associated ataxia, the addition of pressure splints possibly has no additional benefit compared with neuromuscular rehabilitation alone (1 Class II study). Data are insufficient to support or refute use of stochastic whole-body vibration therapy (1 Class III study).

4-aminopyridine AKA dalfampridine, Ampyra

- Studies of its use in episodic ataxia suggest that 5mg tid or 10mg bid are as effective in controlling attacks as is acetazolamide 250mg tid.
- Studies of its use in cerebellar ataxia or in downbeat nystagmus show mixed results:
- Experience in a short-term trial with 4-aminopyridine in cerebellar ataxia.Giordano I, Bogdanow M, Jacobi H, Jahn K, Minnerop M, Schoels L, Synofzik M, Teufel J, Klockgether T.J Neurol. 2013 Aug;260(8):2175-6.
- Aminopyridines for the treatment of neurologic disorders.Strupp M, Teufel J, Zwergal A, Schniepp R, Khodakhah K, Feil K.Neurol Clin Pract. 2017 Feb;7(1):65-76.
- GAA-FGF14 ataxia (SCA27B): phenotypic profile, natural history progression and 4-aminopyridine treatment response. Wilke C, Pellerin D, Mengel D, Traschütz A, Danzi MC, Dicaire MJ, Neumann M, Lerche H, Bender B, Houlden H; RFC1 study group; Züchner S, Schöls L, Brais B, Synofzik M.Brain. 2023 Oct 3;146(10):4144-4157.

- Ampyra and its generic time release formulation may not be covered by insurance if the patient does not have MS. Average cash price **$3000 per month,** GoodRx coupon price **as low as $50 per month.**
- A compounding pharmacy can prepare 5mg capsules for use tid for a little over $100 per month.
- High dose (greater than 20mg per day) may cause seizures.

Riluzole 50mg q12h on an empty stomach, monitor LFTs

- December 1995, riluzole (Rilutek) was approved for the treatment of patients with amyotrophic lateral sclerosis. Cost $500/mo self-pay; under $50 with GoodRx coupon.
- Two European studies suggested efficacy in the treatment of ataxia:

- **Riluzole** in cerebellar **ataxia**: a randomized, double-blind, placebo-controlled pilot trial.Ristori G, Romano S, Visconti A, Cannoni S, Spadaro M, Frontali M, Pontieri FE, Vanacore N, Salvetti M.Neurology. 2010 Mar 9;74(10):839-45.
- **Riluzole** in patients with hereditary cerebellar **ataxia**: a randomised, double-blind, placebo-controlled trial.Romano S, Coarelli G, Marcotulli C, Leonardi L, Piccolo F, Spadaro M, Frontali M, Ferraldeschi M, Vulpiani MC, Ponzelli F, Salvetti M, Orzi F, Petrucci A, Vanacore N, Casali C, Ristori G.Lancet Neurol. 2015 Oct;14(10):985-91.

- However a recent study in SCA2 did not show benefit in symptoms or disease progression over one year:

- Safety and efficacy of **riluzole** in spinocerebellar **ataxia** type 2 in France (ATRIL): a multicentre, randomised, double-blind, placebo-controlled trial.Coarelli G, Heinzmann A, Ewenczyk C, Fischer C, Chupin M, Monin ML, Hurmic H, Calvas F, Calvas P, Goizet C, Thobois S, Anheim M, Nguyen K, Devos D, Verny C, Ricigliano VAG, Mangin JF, Brice A, Tezenas du Montcel S, Durr A.Lancet Neurol. 2022 Mar;21(3):225-233.

- Riluzole may cause fatigue, dizziness, somnolence, and vertigo and should be used with caution in ataxic patients.

Long-Term Follow-Up before and during Riluzole Treatment in Six Patients from Two Families with Spinocerebellar Ataxia Type 7.

Agnese Suppiej, Chiara Ceccato, Radouil Tzekov, Iveta Cermakova, Francesco Parmeggiani, Gianmarco Bellucci, Marco Salvetti, Theresa Zesiewicz, Giovanni Ristori, Silvia Romano

Cerebellum. 2024 Dec;23(6):2226-2235.

- **Background:** Currently no curative treatment exists for spinocerebellar ataxias (SCAs). Riluzole repurposing was proposed as a symptomatic treatment in different types of cerebellar ataxia. We report a long-term-follow up under riluzole treatment in SCA type 7.
- **Methods:** Six patients received Riluzole 50 mg twice daily on a compassionate use program for a mean of 4.8 years (range 3.5-9). We measured ataxia onset and progression through the Scale for the Assessment and Rating of Ataxia (SARA), and collected extensive ophthalmological data before and after Riluzole treatment. Electrocardiogram and laboratory profile for drug safety were performed every six months.
- **Results:** Riluzole treatment showed no effect on visual function in two patients with an advanced retinal damage. Improvements of visual function occurred in four patients followed by ophthalmologic stability up to 5 years after starting treatment. Two patients had a less steep deterioration of ataxia after treatment compared to pre-treatment, during the first 2,5 years of therapy. One showed soon after therapy an improvement of the SARA score, and then overall stability lasting 3,5 years, followed by ataxia worsening. One visually impaired patient without neurological impairment did not worse until the last visit after 3,5 years of follow-up. The remaining 2 patients showed an improvement of SARA scores soon after therapy, and an overall stability lasting respectively 5 and 3 years. No adverse event was registered during the observation period.
- **Discussion:** This study suggests a possible beneficial action of Riluzole in SCA7 and provides a detailed description of the ophthalmologic profile of these patients.

BHV-4157 Troriluzole, a Riluzole pro-drug

- Biohaven Pharma is completing a Phase III trial in the common dominant ataxias:
- ClinicalTrials.gov Identifier: NCT03701399--A Phase III, Long-Term, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects With Spinocerebellar Ataxia.
- Phase II trial suggested that 140mg per day dose was too low, 8 week double blind treatment was too short, midline cerebellar symptoms responded better than appendicular, SCA1 and SCA2 responded better than SCA3,6,8,10.
- Phase III trial is using 200mg per day, double blind treatment for a year, preferential midline cerebellar measures and increased SCA3 enrollment suggested measurable benefit.
- Participants in both trials have been eligible to continue in an open-label extension.
- Biohaven has opened an expanded access program for non-participants.

- Benefits of pro-drug—can be taken once a day with or without food, bypasses liver on first pass thus reducing aminotransferase elevations.
- MOA--glutamate transporter modulation at the Purkinje cell, suggesting it should have greater efficacy in the ataxias with predominant Purkinje cell involvement (eg. SCA1, 8).

AAN 2024--**Matching-adjusted Indirect Comparison of Troriluzole Versus Untreated Natural History Cohort in Spinocerebellar Ataxia**

- Melissa Beiner[1], Lauren Powell[2], Basia Rogula[2], Michele Potashman[1], Victoria Wirtz[1], Jeremy Schmahmann[3], Susan Perlman[4], Vladimir Coric[1], Gilbert L'Italien[1]
[1]Biohaven Pharmaceuticals, Inc., [2]Broadstreet HEOR, [3]Massachusettes General Hospital, [4]UCLA School of Medicine

- **Objective:**
- To understand the treatment effect of troriluzole over 3 years in patients with spinocerebellar ataxia (SCA) by conducting a matching-adjusted indirect comparison (MAIC) of troriluzole-treated subjects vs subjects in a pooled natural history cohort.
- **Background:**
- SCAs are rare inherited neurodegenerative disorders characterized by progressive ataxia affecting limb coordination, balance, and speech. BHV4157-206 (NCT03701399) was a pivotal efficacy trial examining troriluzole vs placebo, consisting of a 48-week double blinded period followed by a 3-year open-label extension.
- **Design/Methods:**
- A MAIC was conducted for all SCA genotypes and SCA3 genotype only, to compare ataxia symptoms over 3 years between troriluzole-treated subjects and an untreated natural history cohort. Patient-level natural history data were weighted to match the overall baseline characteristics of troriluzole-treated subjects (modified-functional Scale for the Assessment and Rating of Ataxia [f-SARA], genotype, sex, age, and age of symptom onset). The between-group least squares (LS) mean change from baseline differences on f-SARA were derived, for years 1, 2, and 3.
- **Results:**
- A total of 96 troriluzole-treated subjects and 611 untreated natural history subjects informed the all SCA genotype analysis. LS mean change differences in f-SARA for all SCA genotypes were -0.64, -1.16, and -1.34 at years 1, 2, and 3, favoring troriluzole ($p=0.0008$, <0.0001, and <0.0001 respectively). Thirty-eight troriluzole-treated SCA3 subjects were compared to 205 untreated. LS mean change differences for the SCA3 genotype were -0.75, -1.11, and -1.92, favoring troriluzole ($p=0.0181$, 0.0009, and <0.0001 respectively). These results indicate greater ataxia-related impairment and clinical decline amongst the natural history cohort compared to troriluzole-treated subjects.
- **Conclusions:**
- Compelling and sustained treatment effects were observed out to 3 years when troriluzole-treated subjects were compared to a matched untreated natural history cohort. These results demonstrate that long-term daily dosing of troriluzole attenuates the progression of disease among subjects with SCA3 over 3-years and, to a lesser extent, for all SCA genotypes.

NCT03408080 -- An Open Pilot Trial of BHV-4157 Investigator-initiated IND

- 4 groups—other predominantly cerebellar ataxias, cerebellar ataxia with predominant dizziness, patients with cerebellar ataxia switching from Riluzole, MSA-C. Followed for 24 weeks. SARA monitored.
- Other Cerebellar cohort—10 enrolled, 2 discontinued after 12 weeks (1 c dizziness, 1 p fall c injury), 5 improved.
- Dizzy cohort—4 enrolled, 3 discontinued due to increased dizziness. 1 still dizzy but wanted to continue.
- Switch cohort—4 enrolled, all the same or slightly better than on Riluzole.
- MSA cohort—11 enrolled, 5 discontinued after 12 weeks due to dizziness and incr imbalance (2 c incr PD sxx), 3 minimally improved.

Phenotypic Variation requiring management beyond ataxia and sometimes involvement of other subspecialties

- Common features to most of the common ataxias:
  - Gait ataxia, limb incoordination
  - Dysarthria, dysphagia
  - Eyes: Saccadic pursuit, overshoot, nystagmus, diplopia, ophthalmoplegia
- Features in some ataxias
  - Other ocular disorders—retinal or optic nerve deterioration (SCA1,7; Friedreichs)
  - Extrapyramidal—dystonia, Parkinsonism (SCA2,3)
  - Peripheral nerve—sensory, motor unit (SCA1,2,3)
  - Upper motor neuron—SCA1,3,7; hereditary spastic ataxias; adrenomyeloneuropathy
  - Tremor—SCA2,8,12; FXTAS
  - Intellectual deterioration—SCA1,2,3,12,17,DRPLA
  - Seizures—SCA10
  - Extraneural involvement—cardiac, diabetes or other endocrine, skeletal (Friedreichs, other mitochondrial)

Symptomatic Management of Ataxia

Diagnosis and management of progressive ataxia in adults. de Silva RN, Vallortigara J, Greenfield J, Hunt B, Giunti P, Hadjivassiliou M.Pract Neurol. 2019 Jun;19(3):196-207.

Figure 9 Infographic 2: Symptom Management, including Multidisciplinary Team Input

The National Ataxia Foundation has a factsheet

Medications for Ataxia Symptoms

Depression: SSRI's (Selective serotonin reuptake Inhibitors), SNRI's (Selective norepinephrine-serotonin reuptake inhibitors) – classes of drugs for anxiety or depression

Dizziness/Vertigo: Acetazolamide (Diamox), 4-aminopyridine, Baclofen, Clonazepam, Flunarizine, Gabapentin (Neurontin), Meclizine, Memantine, Ondansetron (Zofran), Scopolamine (eg. Transderm Scop Patch for motion sickness)

Excessive daytime sleepiness: Modafinil (Provigil) or Armodafinil (Nuvigil)

Erectile Dysfunction: Cialis, Levitra, Viagra

Fatigue: Amantadine, Atomoxetine (Strattera), Buproprion (Wellbutrin), Carnitine, Creatine, Modafinil (Provigil) or Armodafinil (Nuvigil), Pyridostigmine, Selegiline (Eldepryl), Venlafaxine (Effexor), Desvenlafaxine (Pristiq); SSRI's (Selective serotonin reuptake inhibitors), SNRI's (Selective norepinephrine-serotonin reuptake inhibitors) – classes of drugs for anxiety or depression that may also help fatigue.

Imbalance/Incoordination: Amantadine, Buspirone (Buspar), Riluzole (Rilutek), Varenicline (Chantix). *(Pilot Study of Varenicline (Chantix®) in the Treatment of Friedreich's ataxia was terminated as a result of concerns regarding safety and intolerability).*

Memory or thinking disorders: Cholinesterase inhibitors (memory drugs approved for use in Alzheimer's disease), Memantine (Namenda)

Muscle cramps or spasms: Baclofen, Tizanidine (Zanaflex)

Muscle strength: Creatine

Myofascial **pain:** Cymbalta, Lyrica, Gabapentin

Neuropathy: Cymbalta, Lyrica; as well as common usage of gabapentin, other anti-seizure drugs, and various tricyclic anti-depressants.

Nystagmus: Acetazolamide (Diamox), 4-aminopyridine, Baclofen, Carbamazepine, Clonazepam (Klonopin), Gabapentin (Neurontin), Isoniazid, Memantine

Orthostatic hypotension: Atomoxetine (Strattera), Droxidopa (Northera), Ephedrine, Fludrocortisone (Florinef), Midodrine, Pyridostigmine

Overactive Bladder: There are many anticholinergic drugs approved for overactive bladder, which can help in cases of neurogenic bladder. Botulinum toxin Shots have also been used in severe cases unresponsive to oral medication or rehabilitation/biofeedback strategies.

Restless legs: Gabapentin (Neurontin or Horizant), Levodopa (carbidopa-levodopa, Sinemet), Pramipexole (Mirapex), Ropinirole (Requip)

Rigidity: Pramipexole (Mirapex), Ropinirole (Requip)

Sleep Disorders/Parasomnias (vivid dreams, nightmares, acting out dreams, sleep talking): Clonazepam. **Sleep apnea symptoms** must be evaluated with a sleep study (nocturnal polysomnogram) and treated with positive pressure airway support if indicated.

Speech and Swallowing: pseudobulbar dysfunction --Fluoxetine (Prozac), NAC (N-acetylcysteine)

Stiffness/Spasticity/Rigidity/Dystonia: Amantadine, Baclofen, Botulinum toxin Shots, Dantrolene sodium (Dantrium), Diazepam (Valium)- (But high doses can worsen ataxia), Levodopa (carbidopa-levodopa, Sinemet), Pramipexole (Mirapex), Ropinirole (Requip), Tizanidine (Zanaflex), Trihexyphenidyl

Tremor or Rest Tremor: Amantadine, Botulinum toxin Shots, Carbamazepine, Clonazepam, Deep Brain Stimulation, Flunarizine, Gabapentin (Neurontin), Isoniazid, Levetiracetam, Levodopa (carbidopa-levodopa, Sinemet), NAC (N-acetylcysteine) Ondansetron (Zofran), Pramipexole (Mirapex), Primidone, Propranolol, Ropinirole (Requip), Topiramate, Valproic Acid (Depakote)

Uncontrolled Laughing and Crying: Fluoxetine (Prozac), Neudexta, Amitriptyline

Episodic Ataxia type 1: Carbamazepine, Phenytoin

Episodic Ataxia type 2: Flunarizine, Acetazolamide, and 4 aminopyridine

A Checklist of Medications that Could be Tried

Many of them, if you read the fine print, have side effects of ataxa, dizziness, tiredness

1. ImmunoRx
Corticosteroid
Solumedrol
Prednisone
Mycophenolate mofetil (CellCept)
Rituximab
Plasmapheresis
IVIg

2. Anti-oxidants
Alpha lipoic acid
Coenzyme Q10
Creatine
L-carnitine
N-acetylcysteine
Omega 3 fish oil/EPA (eicosapentanoic acid)
Selenium
Vitamin E (d-alpha tocopherol succinate)

3. Ataxia
Acetazolamide
Amantadine
Buspirone
Gabapentin
L-5-OH tryptophan
Riluzole
Thyrotropin releasing hormone
Varenicline (Chantix)

4. Action tremor
Carbamazepine
Clonazepam
Gabapentin
Isoniazid
Levetiracetam
Ondansetron
Primidone
Propranolol
Topiramate
Valproate
Zonisamide

5. Nystagmus Dizziness or other Central Vestibular Sxx
Acetazolamide
Amitriptylene
Baclofen
4-aminopyridine 3,4-diaminopyr”
Carbamazepine Or **Oxcarbazepine**
Clonazepam
Diazepam

Gabapentin
Meclizine
Memantine
Ondansetron
Promethazine
Scopolomine Transdermal patch
Trihexyphenidyl
Valproate
Venlafaxine
Verapamil
Billed cap
Sunglasses

Fatigue is common in cerebellar ataxia, possibly on a central basis

These issues should be sought and managed:

- Underlying medical issues (anemia, nutritional deficiencies, diabetes, cardiovascular or pulmonary problems, rheumatologic disease)
- A sleep disorder could contribute (obstructive or central apneas, periodic leg movements, restless legs, REM sleep disorders, pain, anxiety, depression)
- Some medications may have fatigue as a side effect
- Depression can appear as fatigue or apathy
- Deconditioning could contribute—non-fatiguing exercise could help
- While “energizing” vitamins, supplements, herbs, and stimulant prescription drugs may give some relief of fatigue--long-term side effects, risk of dependence, or drug interactions frequently occur. Use of these should be monitored.

References:

- Evans WJ and Lambert CP. Am J Phys Med Rehabil. 2007 Jan;86(1 Suppl):S29-46
- Weyandt LL, et al. Exp Clin Psychopharmacol. 2016 Oct;24(5):400-414.

Trials that are not moving forward at present in the US

- Biohaven Verdiperstat for MSA (is in an OLE from the Phase 3 study)
- Sanofi Venglustat for late onset Tay Sachs disease (despite positive biomarkers)
- Seelos intravenous trehalose for SCA3 (despite favorable prior data)
- Steminent intravenous stem cells for SCA (studies continue in Asia)
- ASO studies for Spinocerebellar Ataxia types 1 and 3 (although Vico is engaged in its Phase 1 ASO studies for SCA1 and SCA3 and other companies are in pre-clinical development for this).

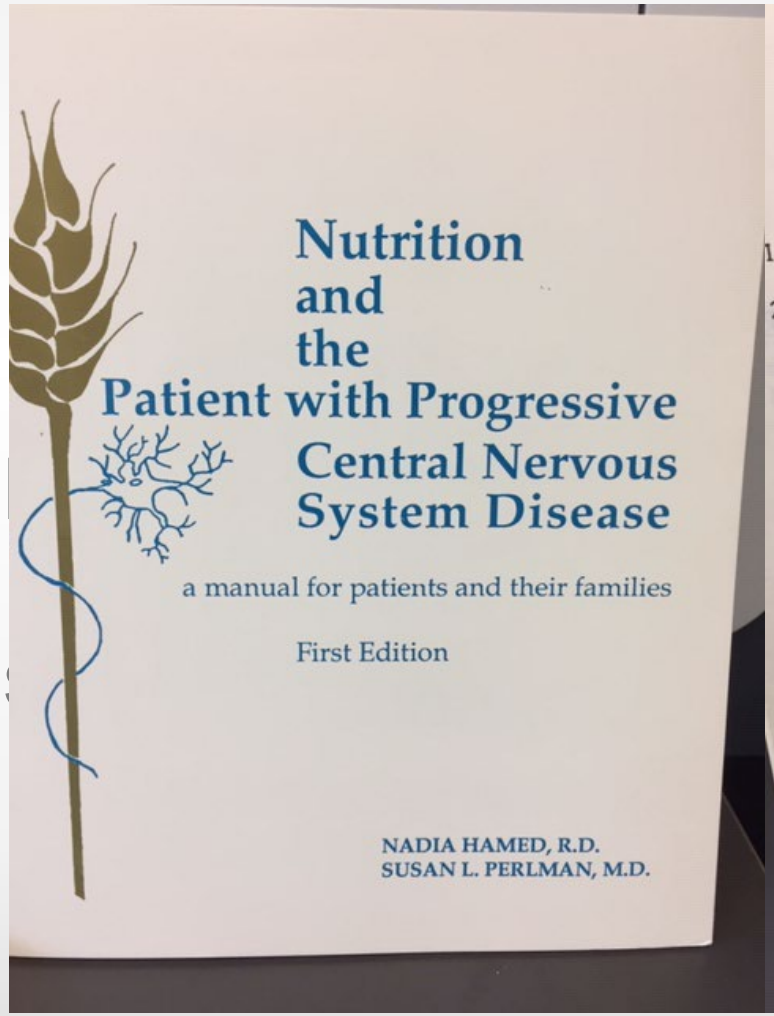
Progress to Track over the upcoming months

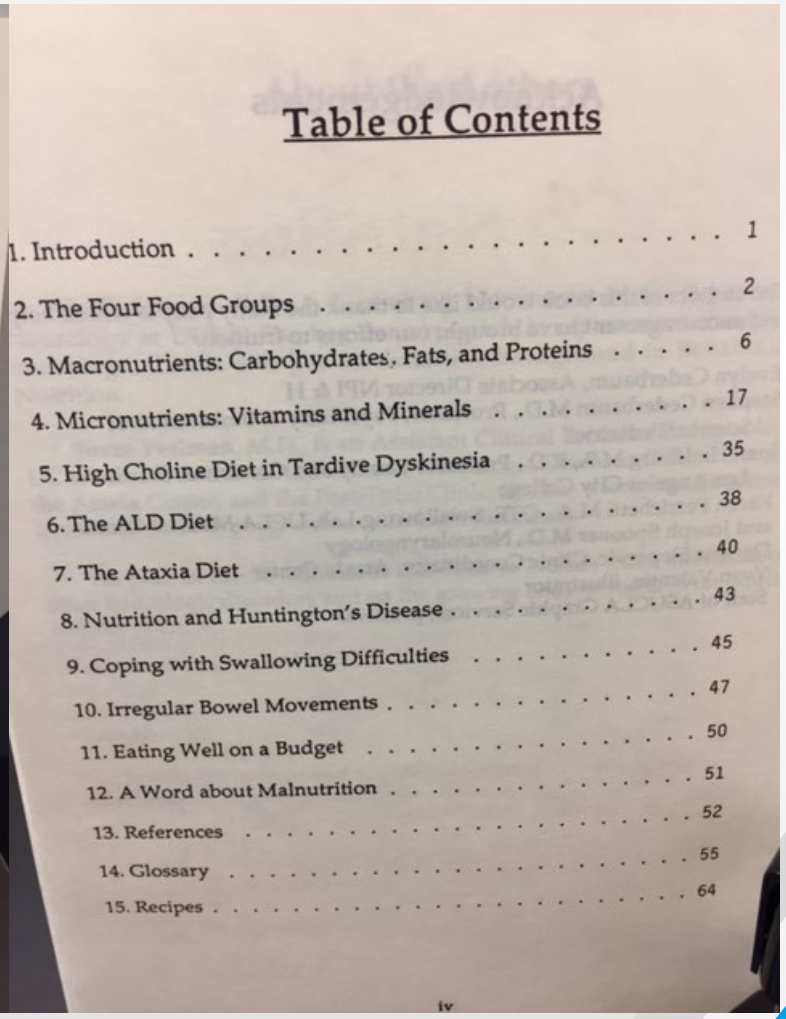
- Biohaven Pharmaceuticals continues to work closely with the FDA on its NDA for Troriluzole in Spinocerebellar Ataxia and is opening an Expanded Access Program for this indication.
- Biogen continues to work with Skyclarys to expand worldwide drug availability, to assess longterm benefits, and to assess its safety, tolerability, and efficacy in the FA population under age 16.
- PTC Therapeutics is engaged in further analysis of its Phase 3 data for Vatiquinone in FA.
- Larimar has started its open label extension of CTI-1601 in FA patients who completed participation in its earlier studies and has started a Phase 1 trial for children.
- Gene replacement trials for FA cardiomyopathy and neurologic involvement.
- Quince Therapeutics has opened enrollment for the Phase 3 NEAT trial in Ataxia Telangiectasia. This pivotal clinical trial will be conducted under a Special Protocol Assessment (SPA) that has been agreed with the U.S. Food & Drug Administration (FDA), which should allow for the submission of a New Drug Application (NDA) following completion of this single study.
- MSA trials that are in Phase 2/3 progress (Lundbeck, Takeda, Alterity, Teva, ONO, Yoda, stem cell).
- The FDA's approach to clinical trials for conditional approval based on primary outcome measures that are biomarkers for target engagement or drug response.

DIET FOR ATAXIA

1. Over 25 Years Ago

“The Ataxia Diet”





Key Features

- Elimination of refined flour and sugar products—use of complex carbs instead.
- Elimination of processed meats.
- Obtain fat from lean meat, poultry, low fat dairy products.
- No skipping meals.
- Benefits that indirectly helped ataxia—weight loss, reduced fatigue, improved constipation, better mood.
- NAF has a Fact Sheet about nutrition and ataxia—
  - https://ataxia.org/wp-content/uploads/2017/07/Ataxia_Diet_FAQ.pdf

2.

There is No Dietary Cure for Regular Ataxia

Inborn Errors of Metabolism that CAN be Treated with Diet or Supplements

Silva et al. Orphanet Journal of Rare Diseases (2019) 14:51
https://doi.org/10.1186/s13023-019-1013-9

Orphanet Journal of Rare Diseases

REVIEW Open Access

Guidelines on the diagnosis and management of the progressive ataxias

Rajith de Silva[1], Julie Greenfield[2], Arron Cook[3], Harriet Bonney[2], Julie Vallortigara[2], Barry Hunt[2] and Paola Giunti[3*]

Table 6 Treatable causes in children

6.1 Glucose transporter 1 deficiency

Recommendation

If Glut-1 DS is diagnosed treat with a ketogenic diet.

6.2 Hypobetalipoproteinaemia

Recommendations

Consider management of the moderate form of hypobetalipoproteinemia by reducing the proportion of fat in the patient's diet and vitamin E supplementation.

6.3 Hartnup disease

Recommendation

Consider treating Hartnup disease with nicotinamide or tryptophan-rich diet, and advise patients on a high protein diet, sunlight protection and avoidance of photosensitizing drugs.

6.4 Biotinidase deficiency

Recommendation

Treat patients diagnosed with biotinidase deficiency with biotin.

6.5 Pyruvate deficiency

Recommendation

Consider treatment with thiamine, carnitine or lipoic acid and advising on a ketogenic diet.

Acquired Causes of Ataxia that Can Be Treated with Diet or Supplements

Table 5 Treatable ataxias

5.1 Gluten ataxia

Recommendation

It is recommended that patients with idiopathic cerebellar ataxia are tested for gluten sensitivity.

Consider testing for antibodies against TG6 (when possible) as a more sensitive test for gluten ataxia.

Ataxia patients with or without enteropathy who have serological evidence of gluten sensitivity should be advised to start a gluten-free diet without delay.

Patients who are starting a gluten-free diet should be advised about strict adherence and given dietetic advice.

Close monitoring is recommended with six-monthly testing to ensure for elimination of antigliadin antibodies.

5.2 Ataxia with vitamin E deficiency

Recommendation

Patients diagnosed with ataxia with vitamin E deficiency or abetalipoproteinemia should be treated with vitamin E supplements.

5.3 Ataxia with vitamin B12 deficiency

Recommendation

Patients diagnosed with ataxia and Vitamin B12 deficiency should be treated with Vitamin B12.

5.4 Ataxia with CoQ10 (ubiquinone) deficiency

Recommendation

Patients diagnosed with ataxia with CoQ10 deficiency should be treated with CoQ10 supplements.

Consider treatment of patients diagnosed with AOA1 with CoQ10 supplementation.

Regular Ataxia (Genetic or Non-Genetic) Seems to Be Associated with Aging

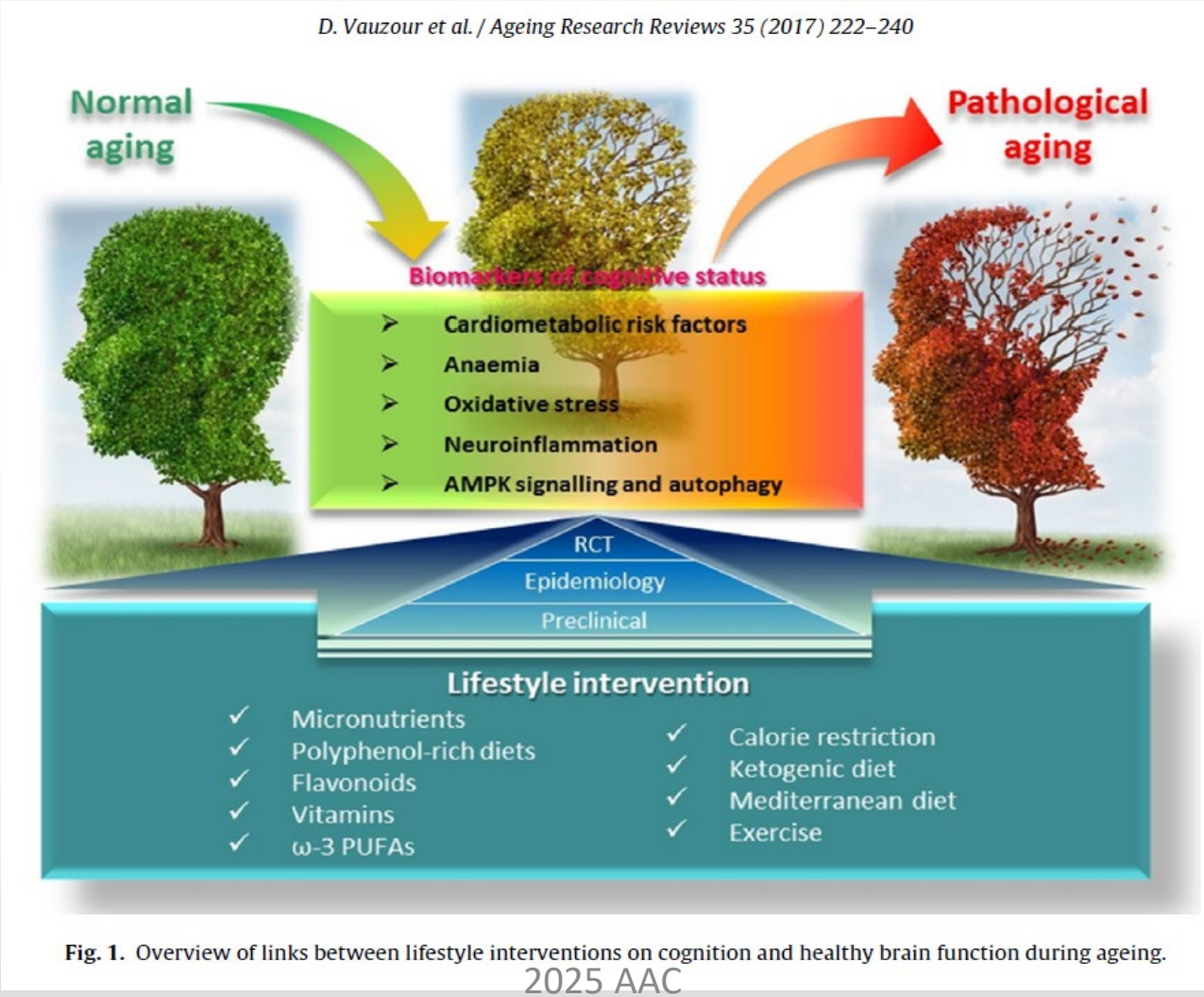


Fig. 1. Overview of links between lifestyle interventions on cognition and healthy brain function during ageing.

Anti-Aging Diets

118,000,000 Google Hits

Risks of Trying Out a Popular Diet for Weight Loss, Aging, or Other Aims

- They promise too much, set unrealistic goals.
- They cost too much.
- Because they often cut out key foods, popular diets may cause the following symptoms:
  - Dehydration.
  - Weakness and fatigue.
  - Nausea and headaches.
  - Constipation.
  - Inadequate vitamin and mineral intake.

Consider consulting with a knowledgeable dietician.
A 6-12 week trial should be a good starting point.

WEIGHT LOSS MEDICATIONS

- Stimulants (also used for fatigue) may contribute to acute adverse physiologic effects including loss of appetite, insomnia, weight loss, headache, nausea, vomiting, abdominal cramps, increased blood pressure and heart rate, and, potentially, worsening of motor tics or tremors.
- GLP1 drugs may cause:
- Gastrointestinal: nausea, vomiting, diarrhea, constipation, and abdominal pain.
- Endocrine: Hypoglycemia (low blood sugar), Pancreatitis (inflammation of the pancreas), and Thyroid C-cell tumors (rare).
- Other: Injection site reactions (redness, pain, swelling), Increased risk of gallstones, Worsening of pre-existing kidney disease, Increased risk of diabetic retinopathy (eye damage)
- Rare but serious side effects: Acute kidney injury, Gastroparesis (delayed stomach emptying), and Bowel obstruction.

Gluten-Free Diet

Avoid—Wheat, Wheat germ, Rye, Barley, Bulgur, Couscous, Farina, Graham flour, Semolina, Spelt, Triticale

- Read labels.
- If you go completely gluten free, you might become deficient in B vitamins, calcium, and iron.

Wahl Anti-Inflammatory Diet

- First proposed for Multiple Sclerosis where the primary mechanism is immune-mediated inflammation.

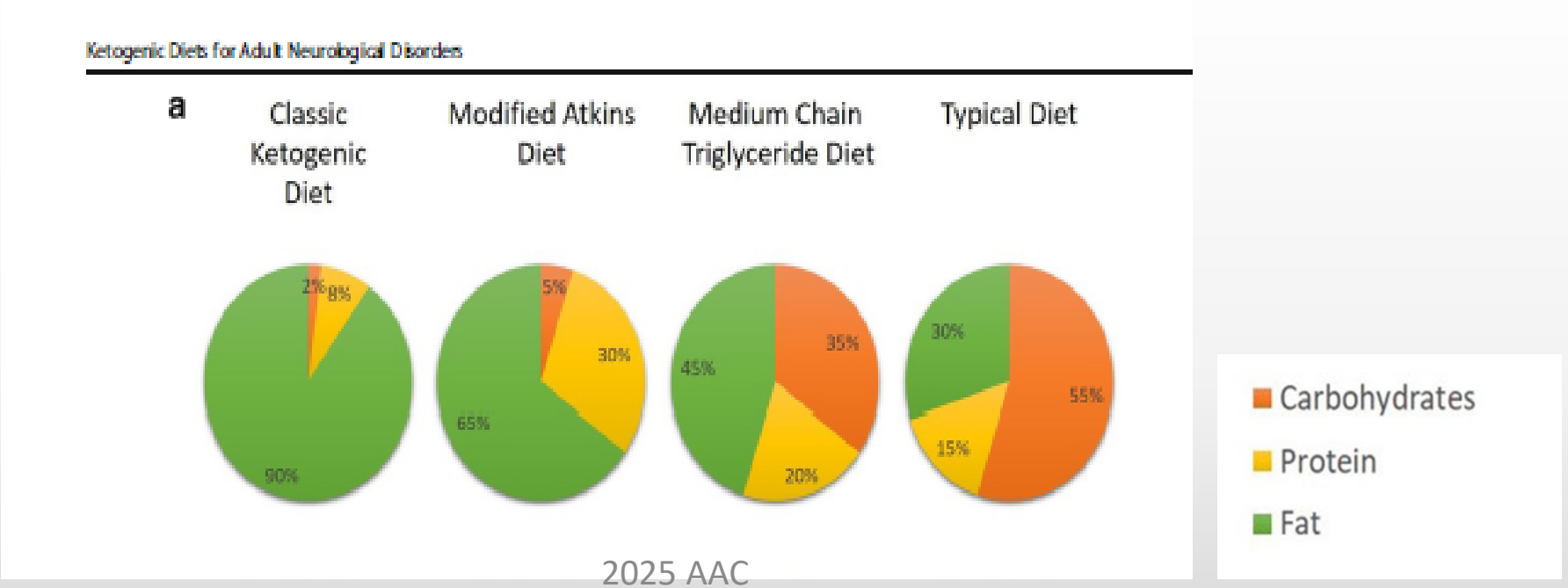
The diet is a version of the Paleolithic (Paleo) diet, based on the idea that humans should eat more like our ancient ancestors and avoid the foods we started eating in the past several hundred years, like wheat and processed foods, which can trigger inflammation.

On the Wahls Protocol, you eat lots of:
Meat and fish
Vegetables, especially green, leafy ones
Brightly colored fruit, like berries
Fat from animal and plant sources, especially omega-3 fatty acids

And avoid:
Dairy products and eggs
Grains (including wheat, rice, and oatmeal)
Legumes (beans and lentils)
Nightshade vegetables, which include tomatoes, eggplant, potatoes, and peppers
Sugar

Intermittent Fasting

- Intermittent fasting is an umbrella term for various eating diet plans that cycle between a period of fasting (16 h) and non-fasting (8 h). It produces intermittent ketosis (cf. Keto Diet; Adkins Diet; Paleo Diet). Intermittent fasting is under preliminary research to assess if it can produce weight loss. Ketosis is also used in childhood drug resistant epilepsy and certain metabolic conditions (ALD/AMN; pyruvate problems)



Curr Neuropharmacol. 2017;15(1):166-173.

Mitochondria and Synaptic Plasticity in the Mature and Aging Nervous System.

Todorova V[1], Blokland A.

J Gerontol A Biol Sci Med Sci. 2015 Nov;70(11):1334-42. doi: 10.1093/gerona/glv070. Epub 2015 May 20.

Reconsidering the Role of Mitochondria in Aging.

Gonzalez-Freire M[1], de Cabo R[2], Bernier M[2], Sollott SJ[3], Fabbri E[4], Navas P[5], Ferrucci L[2].

- Mitochondria produce energy for nerve cells
- Mitochondria promote nerve cell connectivity
- Mitochondria help protect from nerve cell death
- Mitochondria are weakened by many forms of ataxia, genetic and non-genetic.

The “Mitochondrial Diet”

- Ketogenic diet
- Intermittent fasting
- Increased intake of mitochondrial co-factors (coenzyme Q10)
- Much research is ongoing in this area.

Who Should Take Vitamins?

- People over 50--Vitamin D, Vitamin B_{12}, folate.
- Frail elderly may benefit from a low-dose multivitamin supplement.
- Women of child-bearing age--Folic acid and vitamin D, possibly iron.
- Children with a balanced diet may not need vitamins (?Ca++, Fe)
- Multivitamins don't reduce the risk for heart disease, cancer, cognitive decline (such as memory loss and slowed-down thinking) or an early death.
- Vitamin E and beta-carotene supplements appear to be harmful, especially at high doses.

- Probiotics have been popular to regulate the “gut microbiome” and help with gastrointestinal problems. Research is ongoing about the role of the healthy gut microbiome in brain health.

Weight Loss in Chronic Disease

- Unintentional weight loss of **10 pounds** (**4.5 kilograms**) OR 5% of your normal body weight over 6 to 12 months is of concern.
- **Can be due to change in metabolism, decreased appetite, difficulty eating**.
- **Treatment--Increase caloric intake, use an appetite stimulant, consult with your speech and swallowing therapist**.

Useful Websites for patients and practitioners

- http://www.ncbi.nlm.nih.gov for PubMed, OMIM, GeneClinics, GeneReviews
- http://www.neuro.wustl.edu/neuromuscular Neuromuscular Home Page
- https://www.ncbi.nlm.nih.gov/gtr/ Genetic Testing Registry
- http://www.curefa.org Friedreich's Ataxia Research Alliance--FARA

  Links to FA Registry, Natural History and Cardiac studies, Parent and Patient support networks (FAPG, AAPG)
- http://www.ataxia.org National Ataxia Foundation

Thank You

- National Ataxia Foundation
- Friedreich's Ataxia Research Alliance
- The Smith Family Foundation; The Lapin Family Fund; The Bettencourt Fund; The John Paul Fund; The Wapner Family Fund

- And to our patients and their families for their willingness to work with us and to share with us their ideas and hopes.