REVIEW

Key Interventions in Friedreich's Ataxia and Their Impact on Patient Outcomes: A Systematic Review

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ABSTRACT: Friedreich's ataxia (FA) is a rare neurodegenerative disease with multisystemic symptoms that requires multidisciplinary care. This systematic review summarizes available pharmacological and nonpharmacological interventions, their outcomes, and alignment with patient-centered care domains, as well as their impact on these domains. The publication search was conducted in three databases (PubMed, Embase, Cochrane Library) from 2010 to 2025 for human studies. Studies were included if they met predefined eligibility criteria (FA population/pharmacological or nonpharmacological interventions/use of comparator/any outcomes, especially patient reported). All study designs were included. Risk of bias assessment was performed by two reviewers using Cochrane RoB-2 for randomized controlled trials and JBI Critical Appraisal Tools for case reports, case series, and quasi-experimental studies. Results were synthesized narratively. Ninety studies (69 FA only, 21 mixed ataxia) were included. FA-only studies included randomized controlled trials (32%), quasi-experimental studies (35%), and case reports (33%), mostly with small samples (<100) and low-to-moderate bias. Pharmacological interventions (66.7%), mainly disease modifying (93.5%), were more common than nonpharmacological interventions, with the most effective interventions being omaveloxolone (pharmacological), as well as rehabilitation and heart interventions (nonpharmacological). Pharmacological studies often showed biological improvements without clear clinical benefit, whereas nonpharmacological therapies yielded more consistent patient-relevant gains, although evidence was limited. Physical health was the most frequently addressed domain (42.3%), whereas mental health and caregiver aspects were rarely studied (1.8% and 1.4%). No study investigated caregiver burden or economic outcomes. More holistic studies are needed, integrating patient- and caregiver-reported outcomes and combining multiple treatment approaches in larger cohorts. © 2026 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Friedreich's ataxia; intervention; rehabilitation; pharmacotherapy; patient-reported outcomes; quality of life

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Relevant conflicts of interest/financial disclosures: Nothing to report. Author disclosures are available in the Supporting Information

Funding agencies: J.F. was supported within the Advanced Clinician Scientist Programme (ACCENT, funded by the Federal Ministry of Research, Technology and Space [BMFTR] under the funding code [FKZ]: 01EO2107); as a principal investigator (PI) of the iBehave Network, sponsored by the Ministry of Culture and Science of the State of North Rhine-Westphalia; received funding from the National Ataxia Foundation (NAF); and is a member of the European Reference Network for Rare Neurological Diseases. M.G.-E. received research support from the NAF and Ataxia UK, and the European Joint Program for Rare Diseases (EJP-RD) 2021 Transnational Call for Rare Disease Research Projects with local funding from the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (Award 01GM2110). B.M. was supported by Gemeinsamer Bundesausschuss (G-BA), Bundesministerium für Bildung und Forschung (BMBF), Deutsche Demenzhilfe, and EuroQol. T.K. is receiving research support from the Bundesministerium für Forschung, Technologie und Raumfahrt (BMFTR), Servier, and UCB. All funding is unrelated to this study; the study did not receive any external financial support.

Received: 10 December 2025; **Revised:** 12 June 2026; **Accepted:** 17 June 2026

Published online 7 July 2026 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.70423

Friedreich's ataxia (FA) is a rare neurodegenerative genetic disorder with a prevalence between 1:200,000 and 1:750,000 in Europe[1]; it is the most common autosomal recessive ataxia, most frequently caused by a GAA trinucleotide repeat expansion in the frataxin (FXN) gene. The expanded GAA ultimately leads to decreased frataxin protein levels, and thus to iron accumulation in mitochondria, increased oxidative stress, and cell degeneration.[2,3] Depending on the length of GAA1 repetitions, the disease onset can occur either earlier in childhood (longer expansion) or later in adolescence (shorter expansion).[4] The age at onset is also inversely correlated with disease severity, where faster progression and earlier loss of ambulation are observed in patients with early onset.[4-6]

FA is a multisystemic, progressive disease with neurological core symptoms, including ataxia, dysarthria, sensory loss, muscle weakness, and spasticity, as well as nonneurological symptoms such as cardiomyopathy, diabetes mellitus, scoliosis, and pes cavus.[2,7-11] Mental disorders and decline in cognitive functions also occur in the course of the disease.[12-14] Caregivers of patients with FA also report worries and uncertainty about their loved ones, as well as managing their care, representing a substantial caregiver burden.[15] All mentioned symptoms, burdens, and challenges notably influence patients' and caregivers' quality of life.[15,16]

FA requires complex treatment, care, and support. Therefore, several pharmacological and nonpharmacological approaches exist,[2,17] with a primary focus on physical health and clinical outcomes. Since 2024, omaveloxolone has been approved in both the United States and the European Union as the first disease-modifying treatment for FA,[18,19] representing an important milestone.[20,21]

Due to the variety of symptoms and available interventions, a summary of all available evidence about existing interventions in FA would help identify the possible range of treatment options. Despite this, little is known about how the interventions affected various health domains, including physical, mental, and psychosocial health, which is summarized as health-related quality of life. Therefore, it is essential to comprehensively capture all existing evidence on interventional approaches in FA to identify key intervention categories and evaluate their impact on patient- and caregiver-related outcomes. However, so far, no systematic review has synthesized the currently available interventions.

Consequently, this study aims to systematically review all available evidence on pharmacological and nonpharmacological interventions implemented in FA, with the objectives of (1) identifying key intervention categories employed in FA, (2) assessing their alignment with core patient and caregiver outcome domains, and (3) evaluating the intervention impact on these outcomes. Understanding these effects is crucial for developing holistic, patient- and caregiver-centered treatment and care strategies in FA.

Methods

This systematic review was performed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*.[22] The PRISMA 2020 checklist was submitted for editorial review.[23]

Protocol and Registration

The protocol for this review was registered in PROSPERO (ID No. CRD420251075597). All predefined steps were followed throughout the whole process to ensure transparency and quality of this review.[24]

Deviations from the Protocol

After registration, two methodological modifications were implemented: the risk of bias tool was changed to better match the study designs, and the planned certainty assessment was not conducted because of substantial heterogeneity of the evidence. All deviations were documented to maintain transparency.

Study Eligibility Criteria

Study eligibility criteria were determined based on the PICOS (Population, Intervention, Comparison, Outcome, Study design) approach for systematic reviews.[22] Inclusion and exclusion criteria are presented in Table S1.

Information Sources and Search Strategy

Three databases were searched: PubMed, Embase, and Cochrane Library (CENTRAL). The pilot search was conducted before the study protocol registration. The search included publications released since 2010, with no language limitation applied, as long as an English abstract was available. Texts from foreign languages were translated into English. Animal, cell, or in silico studies were excluded.

The search strategy was based on the two dimensions: (1) "Friedreich ataxia" and (2) "interventions." The key words used in the first dimension included "Friedreich ataxia" (MeSH), "cerebellar ataxia," "hereditary ataxia," and "progressive ataxia." Because FA is a rare disease, the search also included other ataxias because studies often group several ataxia types together. In the second dimension, key words encompassed a variety of interventions that included both pharmacological and nonpharmacological aspects, such as "intervention," "rehabilitation" [MeSH], "treatment" [MeSH], "training," "exercise," and "therapy."

The search excluded reviews to limit the options for manual screening. Potential eligible publications identified in previous reviews, but not captured by the search

strategy, were manually added. In addition, gray literature was searched through Google Scholar. The searching was finalized on June 3, 2025, for databases and on June 18, 2025, for manual search. The exact search strategy can be found in Table S2.

Study Selection

Publications from the databases search, manual search, and previous reviews were then added to the online tool Rayyan. Duplicates were removed, and both initial (Title/Abstract) and full-text screenings were performed[25] by two reviewers (D.S. and M.B.) against the predefined inclusion and exclusion criteria. Discrepancies were discussed and solved involving the third reviewer (B.M.).

Data Extraction

From the included publications, we extracted data for (1) study identification (author, year of publication, country), (2) characteristics (design), (3) population (sample size, age, FA characteristics), (4) intervention (type, dose, administration, duration), and (5) outcomes (types, domains, categories, outcome measure, result, observation period).

Risk of Bias Assessment

On the basis of the designs of the included studies, we used the Cochrane RoB-2 for randomized controlled trials (RCTs),[26] the JBI Critical Appraisal Tool for quasi-experimental studies,[27] and the JBI Critical Appraisal Tool for case reports and case series[28] for risk of bias assessment, which was performed independently by two reviewers (D.S. and M.B.). In case of discrepancies, the third reviewer (B.M.) was consulted. The results were standardized and presented in a scale in a color-coded manner: ≥75% low risk of bias (green), 50% to 75% moderate (yellow), ≤50% high (red).[29] Because the study design directly influences the general bias of the study, the assessed risk of bias should be considered within a study design, rather than comparing studies with different designs.

Data Synthesis

Due to the heterogeneity of interventions, a narrative synthesis of the gathered outcomes was performed. The interventions were grouped into key categories, and their effects on the outcomes were compared descriptively. In addition, the alignment of the interventions with core outcome domains defined by the International Consortium for Health Outcomes Measurement (ICHOM) (including physical functioning, symptom control, quality of life, mental well-being, and caregiver burden) was assessed.[23] FA affects both children and adults and, like dementia, is a progressive neurodegenerative disease without a cure, requiring increasing medical and informal care over time. Therefore, the existing ICHOM outcome sets for general pediatric health, general adult health, and dementia were used to assess intervention outcome alignment with health domains.

Results

Study Selection

The search yielded 2227 studies, from which 114 were removed as duplicates. After title and abstract screening, 136 publications were eligible for full-text screening. Finally, 90 publications (69 FA only and 21 mixed ataxia population; Fig. 1A) were included in the narrative syntheses. The study selection process is presented on the PRISMA chart in Figure S1.[30]

Study Characteristics

Tables 1 and 2 and Figure 1 describe the characteristics of included studies for FA-only patients, categorized by intervention type. Characteristics for mixed ataxia populations are available in Tables S4 and S5 and Figure S2.

Almost all included studies were written in English (n = 86; 96%), with only four publications written in languages other than English. Most studies with FA-only patients (n = 69) were conducted in Europe (n = 29; 42.0%), North America (n = 15; 21.7%), or were international studies (n = 20; 29%). The majority of studies included pharmacological interventions (n = 69; 66.7%), with only 33.3% (n = 23) investigating non-pharmacological interventions (Fig. 1D).

Most pharmacological studies were quasi-experimental studies (n = 20; 43.5%) or RCTs (n = 19; 41.3%), whereas nonpharmacological interventions were mostly case reports including case series (n = 16; 69.6%) and quasi-experimental studies (n = 4; 17.4%) (Fig. 1F). Considering all studies, the prevalence of RCTs, quasi-experimental studies, and case reports was similar (32%, 35%, and 33%, respectively) (Fig. 1F). Sample sizes were small, with only one pharmacological study having more than 100 patients.

Risk of Bias

Studies differed in levels of bias and strength of evidence, from RCTs with the highest reliability, through the quasi-experimental studies, up to case reports with the highest bias. The summary of risk of bias assessment for specific study designs is presented in Figure 2. The details from the performed assessments are available in Tables S5 to S10 and Figure S3.

The majority of included studies had a low-to-moderate risk of bias. For case reports/series, the bias mostly considered the reporting of adverse events or the clear and full presentation of patients' disease histories. For quasi-experimental studies, the most considerable bias was

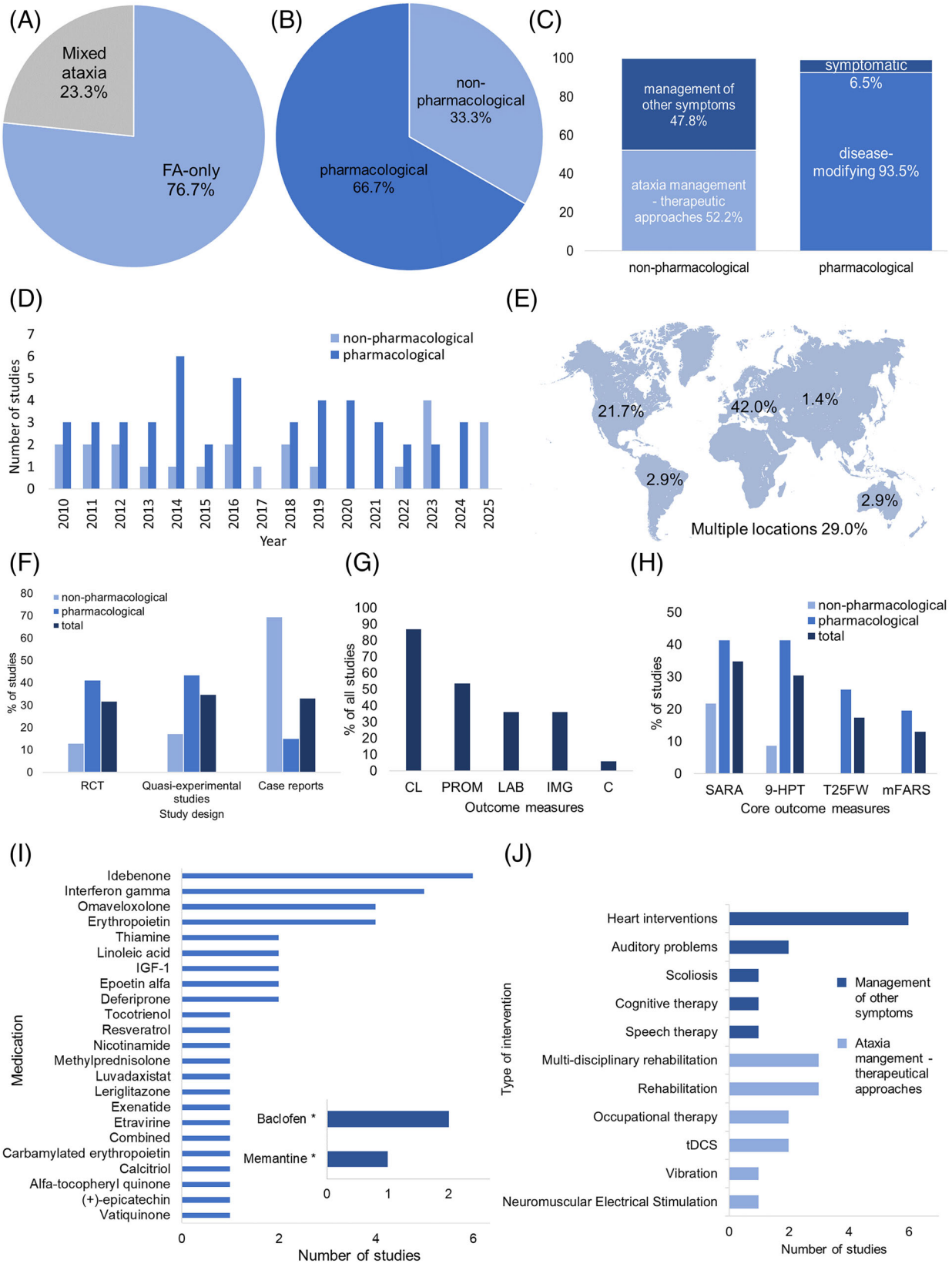


FIG. 1. Legend on next page.

related to internal validity because most studies did not include a control group but instead employed a pre-/post-intervention design. For RCTs, the most concerning aspects were the randomization process and measurement of outcomes, specifically the blinding of assessors and the assessment of outcomes. In addition, RCTs had small sample sizes.

Study Population

FA study participants were children (from 9-year-old patient in case report), young adults with mean age most commonly around 30 years old, up to 65 years old (individual case report). Mostly, the study population had relatively early FA onset, with different ages and, therefore, different disease durations. In mixed ataxia studies, patients with FA represented only a small percentage of study populations and were generally older than in FA-only studies. Other ataxias included in these studies were various types of, for example, autosomal dominant cerebellar ataxia such as spinocerebellar ataxias (eg, types 3, 6, 14, 28), idiopathic late-onset cerebellar ataxia, and multiple system atrophy of cerebellar type, which accordingly varied in their clinical characteristics. Therefore, results cannot be generalized to patients with FA; however, they may provide evidence for potential interventions, which target the ataxia symptoms that are not specific for FA.

Interventions

Pharmacological Interventions

Most pharmacological interventions in FA were disease-modifying therapies (93.5%), with idebenone (13.0%), interferon-γ (10.9%), erythropoietin (8.7%), and omaveloxolone (8.7%) as the most commonly investigated medications (Fig. 1C,I). Symptomatic treatment was described in three case reports (twice intrathecal baclofen for spasms and memantine for optic nerve atrophy). For mixed ataxia studies, in pharmacological interventions, three disease-modifying treatments (vatiquinone and twice riluzole) and one symptomatic treatment (baclofen) were investigated.

As demonstrated in Table 1, 42% of pharmacological RCTs (n = 8) did not show a significant positive effect of the pharmacotherapies, including idebenone (three studies), interferon-γ, erythropoietin, carbamylated erythropoietin, liraglutide, and luvadaxistat, on the investigated outcome measures.[31-38] Similarly, no positive trend of the treatment on outcomes was demonstrated in 15% of quasi-experimental studies on interferon-γ, tocotrienol, and mixed therapy with darbepoetin alfa, idebenone, and riboflavin.[39-41] Other medications such as idebenone,[42] deferiprone in high doses[43] (RCTs), and calcitriol[44] (quasi-experimental study) demonstrated significant increase of ataxia severity (measured with Friedreich's Ataxia Rating Scale [FARS] or International Cooperative Ataxia Rating Scale [ICARS], FARS, and FARS ADL [activities of daily living]) or other outcomes (walking speed).

Although erythropoietin reduced oxidative stress and improved brain structures (imaging and laboratory outcomes), it showed no clear benefit in ataxia severity (Scale for the Assessment and Rating of Ataxia [SARA]) in quasi-experimental studies and no efficacy in an RCT.[36] Methylprednisolone improved patients' global impression in the overall population but showed no significant improvement in other clinical, laboratory, or patient-reported outcomes.[45] In contrast, calcitriol treatment significantly increased frataxin levels but was associated with worsened walking speed.[44]

When observing specific subgroups, pharmacological interventions tended to be more effective in younger, pediatric, and ambulant patients with a shorter disease duration but longer GAA1 repetitions, indicating accelerated disease progression.[34,45-49] Similarly, better effects were reported for patients with lower initial ataxia severity as measured with ICARS or SARA.[43,50]

Nonpharmacological Interventions

Nonpharmacological interventions were rehabilitation, multimodal rehabilitation, occupational therapy, transcranial direct current stimulation, whole-body vibration therapy, and neuromuscular electrical stimulation (52.2%). Specific target symptoms (47.8%) included cardiomyopathy, hearing, scoliosis, cognitive function, or dysarthria (Fig. 1C), with heart intervention (including heart transplantation, septal myectomy, and catheter ablation; 26.1% of all NP interventions) and rehabilitation (26.1%) being the most common treatments (Fig. 1J).

Nonpharmacological interventions showed more consistent positive outcome tendencies compared with pharmacological interventions, with at least one statistically significant or notable improvement in at least one

FIG. 1. Characteristics of included studies. (**A**) Study populations: n = 69 studies for patients with Friedreich's ataxia (FA) only and n = 21 for patients with mixed ataxia. (**B**) Interventions types: n = 46 pharmacological interventions (P), n = 23 nonpharmacological interventions (NP). (**C**) Further division of nonpharmacological interventions. (**D**) Timeline for pharmacological and nonpharmacological studies. (**E**) Geographic location of included studies. (**F**) Study designs of included studies regarding an intervention type and total number of studies. (**G**) Outcome measures used in included studies: CL, clinical; L, laboratory; PROM, patient-reported outcome measure (including subjective and quality of life); IMG, imaging. (**H**) The prevalence of core outcome measures used in included studies: SARA, Scale for the Assessment and Rating of Ataxia; 9-HPT, 9-Hole Peg Test; T25FW, Timed 25-Foot Walk; mFARS, modified Friedreich Ataxia Rating Scale.[113,114] (**I**) Types of pharmacological interventions, n = 46: disease-modifying n = 43, *symptomatic, n = 3. (**J**) Types of nonpharmacological interventions, n = 23: therapeutic approaches for ataxia management, n = 12; and management of other symptoms, n = 11. IGF-1, Insulin-like Growth Factor 1, RCT, randomized controlled trial; tDCS, transcranial direct current stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 *Characteristics of included studies with pharmacological interventions in Friedreich's ataxia (n = 46 studies)*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
Disease modifying:								
Drinkard et al (2010)[32] United States	RCT	42 13.2 ± 2.5 GAA1: 739 ± 230	Idebenone, orally 3 times a day (total dose: 5, 15, 45 mg/kg)	6 months treatment	L	Aerobic capacity	Peak VO_2: 0 ns	Placebo
						Exercise capacity	Peak work rate: 0 ns	
					IMG	Cardiac function	Echo: no relationship between exercise and echo	
Lynch et al (2010)[34] United States, Switzerland	RCT (IONIA)	70 13.7 ± 2.8 DD: 5.55 ± 3.19 y	Idebenone, orally Based on the weight at baseline: 1. 450 mg daily (≤45 kg body weight) or 900 mg daily when >45 kg 2. 1350 mg daily when ≤45 kg or 2250 mg daily when >45 kg	24 weeks (6 months)	CL	Ataxia severity	ICARS: (+) ns	Placebo
						Ataxia severity and functional impairment	FARS: (+) ns	
						Ataxia severity and functional impairment	FACT-Z3: 0 ns	
						ADL	ADL: 0 ns	
Lagedrost et al (2011)[33] United States, Switzerland					CL	Cardiac function	ECG: 0 ns	
					IMG	Cardiac function	Echo: 0 ns	
Meier et al (2012)[42] United States, Switzerland	RCT (IONIA-E)	68 14.0 ± 2.7 DD: 5.5 ± 3.2 y	Idebenone, orally Based on the body weight: 1350 or 2250 mg/day	6-month treatment (controlled study) + 12-month open label	CL	Ataxia severity and functional impairment	ICARS total: (−) ns Subscores speech, posture and stance: (−)[c] FARS total: (−)[c] Subscore speech: (+)[c]	12-month open label
							ICARS total: (+) ns In all subscales: (+),[c] except posture and stance: (−)[c] FARS: (−)[c], subscales speech, lower limb coordination: (+)[c]	18 months (6-month controlled study + 12-month open label)
Cook et al (2019)[46] United Kingdom, Austria, Germany, Netherlands	RCT	29 37.1 ± 16.48[d] DD: 18.39 ± 10.94[d]	Idebenone, orally 1350 mg/day if ≤45 kg, or 2250 mg/day if >45 kg	2 months of treatment or placebo (after the initial 12 months of treatment)	PROM	Perception of change	Change and status questionnaire: 0 ns	Placebo
						Fatigue	MFIS: 0 ns	
					CL	Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Perception of change	CGI-C: 0 ns	
						Speech intelligibility in dysarthria	AIDS: (+)[c]	
						Ataxia severity	ICARS: (+) ns ICARS: (+)[c] for ambulatory patients	
Brandsema et al (2010)[115] Canada	Quasi-experimental	7 15.87 ± 2.21 AaO: 8.5 ± 2.78	Idebenone, orally 20 mg/kg/day twice daily	1-year treatment	PROM (QoL)	QoL	PedsQL total: (+) ns, especially social and emotional scores PedsQL physical: (−)[c]	Pre- and posttreatment
					PROM	ADL	ADL: (+) ns	
					CL	Ataxia severity	ICARS total: 0 ns	
Lynch et al (2019)[35] United States	RCT	92 (51 completed open-label extension)	Interferon-γ, subcutaneously	6-month treatment + open-label phase (1–14 months)	CL	Ataxia severity	FARS: 0 ns **mFARS:** 0 ns	Placebo

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
		16.30 ± 4.10[d] AaO: 9.30 ± 3.83[d]	3 times a week First 4 weeks: weekly dose escalation from 10/25/50/100 μg/m^2			Walking speed and mobility	T25W: 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Vision	LCLA: 0 ns	
						ADL	ADL: 0 ns	
						Perception on disease	CGA: 0 ns	
					PROM	Perception on disease	PGA: n.d.	
						Fatigue	MFIS: 0	
					PROM (QoL)	QoL ≥18 years old	SF-36 n.d.	
					PROM (QoL)C	QoL <18 years old	PedsQL caregiver n.d.	
					L	Frataxin level	Frataxin levels in the whole blood and buccal samples: 0 ns	
					CL	Ataxia severity	**mFARS:** (+) ns	Extension after 52 weeks
					L	Frataxin level	Frataxin levels in the whole blood and buccal samples: (+) ns	
Seyer et al (2015)[57] United States	Quasi-experimental study	12 Mean, range: 12 (8–17) AaO mean: 6	Interferon-γ, subcutaneously 3 times a week Increasing dose: first 2 weeks: 10 μg/m^2; next 2 weeks: 25 μg/m^2; final 8 weeks: 50 μg/m^2	12 weeks of treatment	L	Frataxin level	Frataxin levels in platelets and whole blood: (−),[c] in buccal cell and red blood cells: (+)[c]	Pre-and posttreatment
					CL	Ataxia severity and functional impairment	FARS total: (+)[c], mainly upper extremities subscale	
						Walking speed, mobility	**T25FW:** 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Vision	Visual acuity: (−) ns	
					PROM	Fatigue	MFIS: 0 ns	
						ADL	ADL: 0 ns	
					PROM(QoL)C	QoL	PedsQL: 0 ns (patient and caregiver)	
Marcotulli et al (2016)[41] Italy	Quasi-experimental study	9 29.78 ± 4.94 (21–38)[d] AaO: 16.44 ± 5.17[d]	Interferon-γ, subcutaneously, 3 administrations (at days 0, 14, 28) in doses 100, 150, 200 μg, respectively	28 days of treatment, 35 days of follow-up	CL	Ataxia severity	**SARA:** 0 ns	Pre- and posttreatment
					L	Frataxin level	Frataxin levels: 0 ns	
Vavla et al (2020)[61] Italy, United States	Quasi-experimental study	12 17.33 ± 4.54 AaO: 8.5 ± 3.18	Interferon-γ, subcutaneously Dose escalation: first 2 weeks 100 μg, following 22 weeks 200 μg	6 months of treatment, 6 months after treatment	CL	Ataxia severity	**SARA**—stabilized[c] worsening trend after the discontinuation	Pre- and posttreatment
						Cardiac function	ECG (+)[c]	
					IMG		Echo: 0 ns	
					L	Frataxin level	Frataxin level in PBMCs: (+) ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
Tekin and Levent (2022)[116] Turkey	Case report	1 9 9	Interferon-γ, subcutaneously 3 times a week Dose escalation: 14 days 10 μg/m^2, then 14 days 25 μg/m^2, then 50 μg/m^2	Follow-up: 112 days, 280 days (9 months)	CL	Ataxia severity and functional impairment	FARS: (+)	Pre- and posttreatment
						Manual dexterity and fine motor coordination	**9-HPT:** 0	
						Walking speed and mobility	**T25FW:** 0	
					IMG	Cardiac function	Echo: minimal cardiological deterioration	
Lynch et al (2019)[47] United States, Austria, Australia	RCT MOXIe part 1	69 25.6 ± 6.5 AaO: 15.3 ± 4.8	Omaveloxolone, orally, 2.5–300 mg/day, once daily	12 weeks	CL/L	Dose ranging	Optimal changes observed in doses 80–160 mg daily	Dosage 160 mg/day vs. placebo
					L	Exercise capacity	Peak workload: 0 ns	
					CL	Ataxia severity	**mFARS:** (+)[c]	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Walking speed and mobility	**T25FW:** 0 ns	
						Vision (low contrast)	LCLA: 0 ns	
					PROM(QoL)	QoL	SF-36: 0 ns	
Lynch et al (2021)[48,49] United States, United Kingdom, Austria, Italy	RCT MOXIe study part 2	82 Full analysis set 23.89 ± 7.16[d] AaO: 15.49 ± 5.48[d]	Omaveloxolone, orally, 150 mg daily	48 weeks of treatment + 4 weeks of follow-up (52 weeks to 12 months)	CL	Ataxia severity	**mFARS:** (+)[c] Subscores: upper limb coordination and upright stability	Placebo
					PROM	Perception of change	PGI-C: (+) ns	
					CL	Perception of change	CGI-C: (+) ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Walking speed and mobility	**T25FW:** 0 ns	
					PROM	Frequency of falls	Frequency of falls: (+) ns	
					L	Exercise capacity	Peak workload: (+) ns	
					CL	ADL	FA ADL: (+)[c]	
Lynch et al (2023)[73] United States, Austria, Italy, United Kingdom	Quasi-experimental study	82 23.89 ± 7.16[d] AaO: 15.49 ± 5.48[d]	Omaveloxolone, orally 150 mg daily	72-week extension (16 months) (up to 144 weeks)	CL	Ataxia severity	**mFARS:** (+) stable improvement, no worsening	Placebo
Lynch et al (2024)[86] United States, Italy, Australia, Austria, Switzerland, United Kingdom	Quasi-experimental study	136 from each study FACOMS, MOXIe Mean age: 26.2 ± 13.7; 26.6 ± 7.3 AaO: 15.2 ± 10.5; 15.5 ± 5.3	Omaveloxolone, orally 150 mg daily	Follow-up: FACOMS: 2.54 ± 0.79 years MOXIe: 2.60 ± 0.52 years	CL	Ataxia severity and functional impairment	Long-term (3-year) efficacy of omaveloxolone **mFARS:** (+)[c]	FACOMS natural history data
Mariotti et al (2012)[36] Italy	RCT	16 28.5 ± 5.5[d] AaO: 12.67 ± 4.07[d]	Erythropoietin, intravenously Scaling up 20,000 IU every 3 weeks for 9 weeks, 40,000 IU every 3 weeks for 9 weeks,	6 months of scaling up	L	Frataxin level	Frataxin level: 0 ns	Between groups, Vs. placebo
					CL	Ataxia severity	**SARA:** 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
			and 40,000 IU every 2 weeks for 6 weeks		PROM(QoL)	QoL	SF-36: 0 ns	
Nachbauer et al (2011)[75] Austria	Quasi-experimental study	5 Median age: 49 years (IQR 31–52) Median AaO: 21 years (IQR 10–23)	Erythropoietin, subcutaneously 3 times single injections: 5000 IU, 10,000 IU, 30,000 IU, in 1-month intervals	3 months	L	Frataxin level	Frataxin: (+)[c]	Pre- and postintervention
						Iron metabolism	Reduced ferritin level: (+)[c]	
						Mitochondrial function	Mitochondrial function: 0 ns	
					CL	Ataxia severity	**SARA:** 0 ns	
Egger et al (2014)[117] United States, Germany, Austria	Quasi-experimental study	9 33.11 ± 10.68[d] DD: 11.33 ± 5.43[d]	Erythropoietin, subcutaneously 5000 IU, 3 times a week/2 months + 6 months follow-up 2000 IU 3 times weekly	8 weeks of treatment (for 2 patients 2 weeks) 10–12 months of follow-up	IMG	White matter	DTI: fractional anisotropy in white matter: (+)[c]	Pre- and posttreatment
					CL	Ataxia severity and functional impairment	**SARA:** 7/9 (+) (at least −2 points) FARS: 7/9 (+) (at least −4 points) No correlation between DTI changes and changes in FARS and SARA	
Santner et al (2014)[77] Switzerland, Austria, Germany	Quasi-experimental study	9 33.11 ± 10.68[d] DD: 11.44 ± 5.36[d]	Erythropoietin, subcutaneously 5000 IU, 3 times a week for 8 weeks, then 2000 IU, 3 times a week	Up to 6 months of treatment	IMG	Gray matter volume	MRI VBM: gray matter volume in pulvinar and posterior parietal cortex: (+)[c]	Pre- and posttreatment
					CL	Ataxia severity and functional impairment	**SARA**, FARS improvement correlated with VBM changes	
Costantini et al (2016)[69] Italy	Quasi-experimental study	34 36.3 ± 11.1 AaO: 17.1 ± 9.9	Thiamine (vitamin B_1), intramuscular 100 mg, 2 times a week	Up to 24 months	CL	Ataxia severity	**SARA** total: (+)[c]	Pre-and posttreatment
					PROM	Fatigue	FSS: 0 ns	
					CL	Deep tendon reflexes	Reappearance in 57% of patients with areflexia	
						Swallowing	Improvement in 63% of patients with dysphagia	
					IMG	Cardiac function	Echo +/−	
					L	FXN gene expression	FXN gene expression: 0 ns	
Costantini et al (2013)[118] Italy	Case report	2 (39, 27) AaO: >24 years	Thiamine (vitamin B_1), intramuscular 100 mg every 3 or 5 days	3 months of treatment	CL	Ataxia severity	**SARA:** (+) 58.9%	W39
					PROM	Fatigue	FSS: (+) 57.8%	
					CL	Ataxia severity	**SARA:** (+) 66.7%	M27
						Dysmetria	Dysmetria: (+)	
						Speech	Speech: (+)	
Zesiewicz et al (2018)[62] United States	RCT	19 Median age, range Treatment: 34 (18–48) Comparator: 37 (23–47) AaO: <25 years	Linoleic acid, orally 1.8 g once daily or 4.5 g twice daily	28 days of treatment	L	Aerobic capacity	VO_2 max: (+) ns	Placebo
						Exercise capacity	Peak workload: (+)[c]	
					CL	Ataxia severity and functional impairment	FARS-Neuro: (+) ns	
						Walking speed and mobility	**T25FW:** 0 ns	
Lynch et al (2023)[74] United States, Australia	RCT	65 recruited 45 completed the study	Linoleic acid, orally, 1 capsule 960 mg	11 months of treatment	L	Aerobic capacity	MVO_2: 0 ns	Placebo

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
		19.67 ± 7.99[d] AaO: <26 y	First months: 9 capsules daily (3 × 3 × 3); later, 6 capsules daily (3 × 0 × 3)			Exercise capacity	Peak workload: 0 ns	
					CL	Functional mobility	T1MW: 0 ns	
						Ataxia severity	**mFARS:** (+)[c]	
						Perception of change	CGI-C: 0 ns	
						Gait	GST: 0 ns (T1MW, peak workload, and MVO_2)	
					PROM	Fatigue	In treatment group: modified FACIT: 0 ns	
Sanz-Gallego et al (2014)[119] Spain	Quasi-experimental study	5 26.6 ± 5.4 DD: 9.4 ± 5.5 y	IGF-1 (mecasermin), subcutaneously 50 μg/kg twice a day	12 months of treatment, 3 years of follow-up	CL	Ataxia severity	**SARA** 2/5: (+)/(−)	Pre- and posttreatment 12 months/3 years
					IMG	Cardiac function	Echo: 0 ns	
					PROM(QoL)	QoL	SF-36 3/5 fair satisfaction, 2/5 dissatisfied	
Garcia Ron and Rodriguez Mesa (2020)[68] Spain	Case report	1 17 AaD: 11	IGF-1 (mecasermin), subcutaneously Initially, 0.04 mg/kg twice daily, gradually increased to 0.12 mg/kg twice daily	Up to 36 months of follow-up	CL	Ataxia severity	**SARA** total: (+) (9 points), stable over 36 months	Pre- and posttreatment 3 months/36 months vs. previous time points
					IMG	Cardiac function	Echo: (+)	
					PROM(S)	Self-perceived physical function	Energy level and coordination: (+)	
Sacca et al (2016)[59] Italy	RCT	56 35.8 ± 14.2 AaO: 19.3 ± 9.7 years	Epoetin alfa, subcutaneously 1200 IU/kg every 12 weeks, (4 administrations)	24 and 48 weeks of follow-up	L	Aerobic capacity	VO_2 max at the CPET: (+) ns	Between groups (vs. placebo), 24/48 weeks
						Frataxin level in PBMCs	Frataxin level: 0 ns	
					IMG	Cardiac function	Echo: 0 ns	
					CL	Ataxia severity	**SARA:** 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** (+)[c]/(+)[c]	
					PROM(QoL)	QoL	EQ-5D: 0 ns	
					PROM	ADL	ADL/IADL: 0 ns	
Sacca et al (2011)[76] Italy	Quasi-experimental study	10 29 ± 8.2 AaO: 17.2 ± 6.4 years	Epoetin alfa, subcutaneous 1× 600 IU/kg 3 months washout 1× 1200 IU/kg	Up to 6 months after the last dose	L	Frataxin level	Frataxin levels: (+) (gradual increase 3 months after first dose and up to 6 months after the second dose)	Pre- and posttreatment
						Iron metabolism	Total iron: (+)[c] Ferritin: (+)[c]	
					CL	Cardiac function	ECG: 0 ns	
						Ataxia severity	ICARS: 0 ns At frataxin peak: 0 ns	
					IMG	Cardiac function	Echo: 0 ns	
Pandolfo et al (2014)[43]	RCT	72 18.89 ± 7.73[d]	Deferiprone, orally 20/40/60 mg/kg/day	6 months	CL	Manual dexterity and fine motor coordination	**9-HPT:** 0 ns/0 ns	20 mg vs. placebo/40 mg vs. placebo
						Walking speed, mobility	**T25FW:** 0 ns/0 ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
Belgium, Spain, Italy, Australia, France, Canada		GAA repeat ≥400 on the shorter allele				Vision (low contrast)	LCLA: (−) ns/(−) ns	
						Ataxia severity	ICARS: 0 ns/(−)[c]	
						Ataxia severity and functional impairment	FARS: 0 ns/(−)[c]	
					IMG	Cardiac function	Echo: 0 ns in LVSF, LVEF Echo: (+)[c] LV	
					CL	ADL	FARS ADL: 0 ns/(−)[c]	
						Ataxia severity and functional impairment	Worsening of ataxia and adverse effects	60 mg vs. placebo
Elincx-Benizri et al (2016)[120] Israel	Case series	5 24.0 ± 8.0[d] DD: 14.2 ± 6.3[d]	Deferiprone, orally 20 mg/kg/day in 2/3 divided doses, + idebenone	12–24 months of follow-up	CL	Ataxia severity	**SARA** 2/5: (+)	Pre- and posttreatment (12 and 24 months)
						Ataxia severity and functional impairment	FARS 3/5: (+)	
						Manual dexterity and fine motor coordination	**9-HPT** (R) 3/5: (+) **9-HPT** (L) 2/5: (+)	
					IMG	Cardiac function	Echo 3/5: (+)	
					PROM(QoL)	QoL	SF-36 1/5: (+)	
Lynch et al (2012)[71] United States	RCT	31 31.2 ± 11.7 Shorter triplet repeat length 699 ± 205	A0001 (alfa-tocopheryl quinone), orally 500 or 750 mg twice a day	28 days of treatment	CL	Ataxia severity and functional impairment	FARS (+)[c]/(+)[d] [FARS subscore lower limb (+)[c] for a high dose]	Low dose vs. placebo/high dose vs. placebo
					PROM(QoL)	QoL	SF-36 (PFSLS): (−) ns/0 ns	
					PROM	Fatigue, life satisfaction	MFIS LS: (+) ns in high dose	
					CL	Walking speed, mobility	**T25FW:** 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Perception of disease	GICS LS: (+) ns in high dose	
					PROM	ADL	ADL: 0 ns	
Boesch et al (2014)[31] Austria, Italy, Germany, Denmark	RCT	36 27.8 ± 8.7 DoS: 12.03 ± 5.69[d]	Carbamylated erythropoietin (CEPO), intravenously 325 μg three times/week	2 weeks of treatment Up to 43 days of follow-up after baseline (ataxia measures)	L	Frataxin level in PBMCs and buccal cells, mRNA	Frataxin levels: 0 ns	Between groups
						Oxidative stress	8-OHdG: 0 ns	
					CL	Ataxia severity	**SARA:** 0 ns	
						Ataxia severity and functional impairment	FARS: 0 ns	
						Perception of severity	CGI-S: 0 ns	
Paparella et al (2024)[50] Italy	RCT	35 (30 adults, 5 children) 25.0 ± 7.1 AaO: 11.8 ± 5.7 years	Etravirine, orally, 200 or 400 mg/day	4 Months of treatment Follow-up 4 months posttreatment	L	Aerobic capacity	Peak VO_2: 0 ns	Between groups
						Exercise capacity	Peak workload (+)[c]	
					CL	Ataxia severity	**SARA:** (+)[c] after 2 and 4 months	
					IMG	Cardiac function	Echo: 0 ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
					PROM(QoL)	QoL	SF-36 in vitality: (+)[c] Gradual[c] worsening after the discontinuation	
					PROM	Disability and functioning across life domains	WHODAS: (+) mobility, self-care, life activities Gradual worsening after the discontinuation	
					L	Frataxin levels in PBMCs, mRNA	Frataxin: n.d.	
Pandolfo et al (2022)[37] Belgium, Spain, United States, France	RCT	39 24.0 ± 10.7 AaO: 14.3 ± 7.5 years	Leriglitazone, orally Based on age and sex: 150 mg adult males, 130 mg adult females, 2.2 mg/kg in adolescents (12–17 years old) Dose modification after 4 weeks	48 weeks of treatment (11 months)	IMG	Spinal cord structure	MRI of the spinal cord area C2-C3: 0 ns	Placebo
					IMG	Cardiac function	Echo: 0 ns	
					CL	Cerebellar dysfunction of upper limb	CCFS: (−) ns	
						Ataxia severity	**SARA:** 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						ADL	FARS ADL: 0 ns	
						Perception of improvement	CGI-I: 0 (but n.i.)	
						Perception of severity	CGI-S (but n.i.)	
					PROM	Perception of improvement	PGI-I (but n.i.)	
					PROM(QoL)	QoL	EQ-5D-5L: 0 ns	
Wang et al (2021)[38] United States	RCT	67 (63 completed a study) 31.07 ± 10.22[d] A disease stage 2–5 according to FA functional disability stage	Luvadaxistat, orally 75 or 300 mg twice daily	12 weeks of treatment + phone follow-up	CL	Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	Placebo
						Ataxia severity	**mFARS-Neuro:** (+) ns	
						Walking speed and mobility	**T25FW:** 0 ns	
						ADL	FARS ADL: 0 ns	
					PROM	Perception of severity	PGI-S: 0 ns	
					CL	Perception of improvement	CGI-I: 0 ns	
						Perception of severity	CGI-S: 0 ns	
						Vision (low contrast)	LCLA: 0 ns	
					PROM(S)	Self-perceived physical function	No changes/no help (63%), improvement in the upper extremity motor function and manual dexterity during the trial (37%)	
Zesiewicz et al (2018)[72] United States	RCT	63 29.17 ± 7.61[d] Sum of GAA repeats: 1442 ± 301.4[d]	Vatiquinone, orally 200 or 400 mg 3 times daily	24 months (6 months placebo controlled, 18 months open label)	CL	Vision (low contrast)	LCLA: 0 ns	Placebo after 6 months
						Ataxia severity	FARS-Neuro: 0 ns	Lower dose vs. placebo
						Walking speed and mobility	**T25FW:** 0 ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
					IMG	Cardiac function	Echo: 0 ns	
					CL	Ataxia severity	FARS-Neuro: (+)[c] 73% (vs. 43) ≥ 3 points, 64% (vs 33) ≥ 5 points	
						Ataxia severity	FARS: (+)[c]	After 24 months, natural history data
Alemany-Perna et al (2024)[44] Spain	Quasi-experimental study	20 (15 patients received treatment) 29.8 ± 13.9[d] AaO: 16.90 ± 9.27 years[d]	Calcitriol, orally, (active form of vitamin D) 0.25 μg once a day	12 months of treatment	CL	Ataxia severity	**SARA:** (−) ns	Pre- and posttreatment
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Walking speed	8-MWT: (−)[c]	
						Speech motor control	PATA test: 0 ns	
						Independence in daily activities	Barthel Index: 0 ns	
					PROM(QoL)	QoL	SF-36 total: 0 ns [subscore: reported health transition (+)[c]]	
					L	Frataxin level	Frataxin levels (+)[c]	
Arpa et al (2013)[39] Spain	Quasi-experimental study	9 28 ± 8 DD (n = 8): 15.5 ± 9.9[d]	Darbepoetin alfa, route of administration not specified (subcutaneously or intravenously) 150 μg every 2 or 3 weeks Idebenone, orally 10–20 mg/kg/day, twice daily Riboflavin, orally 10–15 mg/kg/day, twice daily	Mean treatment (range) 32 ± 19.4 months (8–56)	CL	Ataxia severity	**SARA:** 0 ns	Pre-and posttreatment, 2 years
					PROM(QoL)	QoL	SF-36v2 44.4% felt better (2 years), 22.2% dissatisfied	
					IMG	Cardiac function	Echo: +/−	
					CL	Ataxia severity	**SARA:** (+)	Vs. annual worsening rate
Qureshi et al (2021)[121] United States	Quasi-experimental study	10 14.5 years (10–22) DD mean: 4.5 years	(+)-epicatechin, orally 75 mg daily (150 mg daily at 12 weeks, when no improvement)	24 months of treatment	CL	Ataxia severity and functional impairment	FARS/**mFARS:** (+) ns FARS: 56% (+)	Pre- and posttreatment
						Walking speed	8-MTW: 33% (+)	
						Manual dexterity and fine motor coordination	**9-HPT:** 60% (+)	
					IMG	Cardiac function	Echo: 0 ns	
						Spinal cord	DTI anisotropy: 0 ns	
Igoillo-Esteve et al (2020)[122] Belgium, Italy, United States	Quasi-experimental study	16 32 ± 3 AaO: 14 ± 1	GLP-1 analogues, subcutaneously Exenatide: 5 μg twice daily—1 week, 10 μg twice daily—4 weeks Or liraglutide: 0.6 mg once daily, 1.2 mg/kg once	5-week GLP-1 analogue treatment; and 4-week washout	L	Frataxin expression in PBMCs and platelets, mRNA	Frataxin levels: (+)	Pre- and posttreatment, exenatide
					CL	Ataxia severity	**SARA:** 0 ns	
						Noncerebellar signs	INAS: 0 ns	
						ADL	ADL: 0 ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
			daily—next 2 weeks, 1.8 mg/kg—last 2 weeks					
Patel et al (2019)[45] United States	Quasi-experimental study	11 (8 children, 3 adults) Median (range): 12 years (9–65) GAA repetition, short allele: 99–900	Methylprednisolone, orally At baseline, 48 mg (6 × 8-mg tablets), then 7 cycles, 28 days each: 6-day treatment, dose tapering: 8 mg (1 tablet) each day	26 weeks	CL	Walking speed and mobility	**T25FW:** 0 ns	Pre- and posttreatment
						Ataxia severity and functional impairment	FARS: 0 ns	
						Functional mobility	T1MW: (+)[c] in children subgroup	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
					PROM	ADL	ADL: 0 ns	
						Fatigue >18	MFIS: 0 ns	
					PROM(QoL)	QoL >18	SF-36: 0 ns	
					CL	Perception of improvement	CGI: 0 ns	
					PROM	Perception of improvement	PGI: (+)[c] in overall population	
					L	Frataxin level	Frataxin level: 0 ns (n.d.)	
					CL	Ataxia severity and functional impairment	**mFARS:** 0 ns	
Libri et al (2014)[58] United Kingdom, Germany, China, New Zealand	Quasi-experimental study	Phase 1: n = 10; mean age: 33 years AaO: 17.9 ± 8.1 years Phases 2 and 3: n = 10; mean age: 33 years AaO: 21.7 ± 9.5 years	Nicotinamide, orally Phase 1: escalating doses: 0–8 g Phase 2: escalating doses 3.5–6 g for 5 days Phase 3: maximum tolerated doses daily for 8 weeks	Phase 2: 5 days Phase 3: 8 weeks	L	Frataxin level	Dose–response relation with frataxin protein concentration[c]	Phase 1
							Sustained frataxin upregulation	Phase 2, 3 Pre- and posttreatment
					CL	Ataxia severity	**SARA:** 0 ns	
						Composite ataxia scale (8 MW + 9-HPT + PATA)	**SCAFI:** 0 ns	
						Walking speed	8 MW: 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
						Speech motor control	PATA: 0 ns	
						Speech understandability	SIT: 0 ns	
					PROM C	ADL	FARS ADL: (+) ns (caregivers)	
Yiu et al (2015)[60] Australia, Austria, China	Quasi-experimental study	24 34.9 ± 12.7 (low dose) 39.2 ± 7.7 (high dose) 37.05 ± 10.50[d] AaO (years): 15.6 ± 6.1 (low-dose) 19.7 ± 7.7 (high dose) 17.65 ± 7.11[d]	Resveratrol, orally 0.5 or 2.5 g twice daily	12 weeks	L	Frataxin level in PBMCs	Frataxin level: (+) ns/(+) ns	Low dose/high dose
						Frataxin mRNA	FXN mRNA: 0 ns/0 ns	
						Oxidative stress markers	0 ns/(+)[c]	
					CL	Ataxia severity and functional impairment	FARS: (+) ns/(+)[c] (mostly upper limb and bulbar components)	
						Ataxia severity	ICARS: 0 ns/(+)[c] (mostly in posture)	
						Ataxia severity	**SARA:** 0 ns/(+) ns	

(Continues)

TABLE 1 *Continued*

Author (year of publication), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Medication, route of administration/Dosage	Duration of treatment/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator/Reported result
						Functional impairment	FACT Z2, Z3: 0 ns/0 ns	
						Speech assessment	CNC word list: 0 ns/(+)[c]	
					PROM	Impact of FA on daily living	FAIS: 0 ns/0 ns	
					PROM(QoL)	QoL	SF-36-v2: 0 ns/0 ns	
					IMG	Cardiac function	Echo: 0 ns/0 ns	
					CL	Vision (low contrast)	LCLA: 0 ns/0 ns	
						Walking speed and mobility	**T25FW:** 0 ns/0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns/0 ns	
Bolotta et al (2020)[40] Italy Symptomatic treatment	Quasi-experimental study	7 (5 completed the study) 21.43 ± 5.91[d] AaO: 9.57 ± 4.04 years[d]	Tocotrienol, orally 5 mg/kg/day	12 months	CL	Ataxia severity	ICARS: (−) ns	Pre- and posttreatment
					IMG	Cardiac function	Cardiac MRI: (+) ns	
Berntsson et al (2013)[123] Sweden	Case report	1 50 AaD: 31	Baclofen 25 μg—test, then via the ITB-delivery pump, 100 μg daily	2 years Follow-up	PROM(S)	Spasm self-assessment	Relief of spasms	Pre- and posttreatment
Kalyvas et al (2018)[124] Greece	Case report	1 65 AaO: 22	Baclofen 50 μg—test, then intrathecal delivery pump 80 μg daily (80–95 μg/day)	3 years Follow-up	PROM(S)	Spasm self-assessment	Relief of spasms, reduced frequency of spasm	Pre- and posttreatment
						Self-assessment of physical function	Pain relief, sleep improvement	
Peter et al (2016)[125] Austria	Case report	1 24 10	Memantine, orally n.i.	1-year follow-up	L	Optic nerve assessment	OCT: no further loss of the nerve fiber layer	Pre- and posttreatment
						Vision	Visual acuity stable	
					PROM(S)	Subjective assessment	Slight deterioration in vision but clear progression of loss of visual acuity	

[a]FA characteristics: AaO, DD, DoS, DS, AaD, or YsD.
[b]Core outcome measures results: +, improvement; −, deterioration regardless of the treatment; 0, no effect.
[c]Significant effect.
[d]Mean (age at onset, disease duration) calculated from the available data in the publication.

Abbreviations: 8-MWT, 8-Meter Walking Test; 8-OHdG, 8-hydroxydeoxyguanosine (oxidative stress marker); 9-HPT, 9-Hole Peg Test; AaD, age at diagnosis; AaO, age at onset; ADL, activities of daily living; AIDS, assessment of intelligibility of dysarthric speech; C, caregiver; CCFS, Composite Cerebellar Functional Scale; CGA, Clinical Global Assessment; CGI-C/-S/-I, Clinical Global Impression of Change/Severity/Improvement; CL, clinical; CNC, consonant-nucleus-consonant word list; CPET, maximal/the highest oxygen consumption during exercise (Cardiopulmonary Exercise Test); DD, disease duration; DoS, duration of symptoms; DS, disease stage; DTI, diffusion tensor imaging; ECG, electrocardiography; echo, echocardiography; EQ-5D(-5L), EuroQol 5-dimension (5-level) questionnaire; FA, Friedreich's ataxia; FACIT, Functional Assessment of Chronic Illness Therapy Fatigue Scale; FACOMS, Friedreich's Ataxia Clinical Outcome Measures Study; FACT Z2/Z3, Friedreich's Ataxia Composite Test (composite of 2 *Z* scores from 9-HPT and T25FW/composite of 3 *Z* scores from 9-HPT); FAIS, Friedreich Ataxia Impact Scale; FARS, Friedreich Ataxia Rating Scale; FARS ADL, Friedreich Ataxia Rating Scale subscore activities of daily living; FARS-Neuro, Friedreich Ataxia Rating Scale neurological function; FSS, fatigue severity scale; FXN, Frataxin; GAA, guanine–adenine–adenine trinucleotide repeat; GICS LS, global impression of clinical severity (life satisfaction); GLP-1 Glucagon-like Peptide-1; GST, gait speed test; IADL, instrumental activities of daily living; ICARS, International Cooperative Ataxia Rating Scale; IGF-1, Insulin-like Growth Factor 1; IMG, imaging; INAS, inventory of non-ataxia symptoms; IONIA, clinical trial on idebenone; IONIA-E, clinical trial on idebenone - extention; ITB, Intrathecal Baclofen; IQR, interquartile range; L, laboratory; LCLA, low-contrast letter acuity; LV, Left Ventricle; LVEF, Left Ventricular Ejection Fraction; LVSF, Left Ventricular Shortening Franction; mFARS, modified Friedreich Ataxia Rating Scale; MFIS (LS), modified fatigue impact scale (life satisfaction); MOXIe, clinical trial on omaveloxolone; MRI, magnetic resonance imaging; mRNA, messenger RNA; MVO_2, maximum oxygen consumption; n.i., no information; ns, not significant; OCT, optical coherence tomography; PATA, PATA speech task; PBMC, Peripherial Blood Mononuclear Cells; PedsQL, pediatric quality of life inventory; PGA, patient global assessment; PGI, patient global impression; PGI-C/-I/-S, patient's global impression of change/improvement/severity; PROM, patient-reported outcome measure; QoL, quality of life; RCT, randomized controlled trial; S, subjective; SARA, Scale for the Assessment and Rating of Ataxia; SCAFI, Spinocerebellar Ataxia Functional Index; SD, standard deviation; SF-36 (PFSLS), Short Form Health Survey with 36 questions (Physical Functioning subscale); SIT, speech intelligibility test; T1MW, Timed 1-Minute Walk Test; T25FW, Timed 25-Foot Walk test; VBM, voxel-based morphometry; VO_2 max, maximal oxygen uptake; VO_2 peak, peak oxygen uptak; WHODAS, World Health Organization disability assessment schedule; YsD, years since diagnosis.

TABLE 2 *Characteristics of included studies with nonpharmacological interventions in Friedreich's ataxia (n = 23 studies)*

Author (year), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Intervention details	Duration of intervention/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator, reported result
Rehabilitation, physiotherapy, sport								
Seco Calvo et al (2014)[126] Spain	RCT	16 53.31 ± 5.65 AaD: 12.33 ± 1.82	Rehabilitation (physical condition, specific physical condition, prefunctional training, and functional training) + pharmacological treatment	5-year program, 2-year follow-up	CL	Ataxia severity	ICARS: (+)[c]	Between groups after follow-up
						Functional independence	FIM: 0 ns	
					PROM(QoL)	QoL	SF-36: 0 ns	
Milne et al (2018)[66] Australia	RCT	19 36.88 ± 12.26[d] AoO: 14.79 ± 8.59[d]	Rehabilitation (strengthening, postural control, coordination and control, functional mobility, balance training, stretching, cardiovascular fitness)	6 weeks inpatient + 6 weeks home based	CL	Functional independence	FIM: 0 ns	Between groups after 6 weeks
						Ataxia severity	FARS: 0 ns	
						Balance	BBS for ambulant patients: (+) ns	
					PROM	Impact of FA on daily living	FAIS movement subscale: (+)[c] FAIS ADL subscale: 0 ns	
						Perception of change	PGI-C: (+)[c]	
Battal et al (2023)[127] Lebanon, France	Case report	1 26 AaO: 16	Rehabilitation + home adjustment (therapeutic adaptive equipment)	3-Month intervention	CL	Ataxia severity	**SARA:** (+) (−9 points)	Pre- and postintervention
						Functional independence	FIM: (+) (+30 points)	
					PROM(S)	Self-perceived physical function	Feeling stronger, more confident, steadier	
Multidisciplinary therapy/Combined therapy (rehabilitation + other)								
Paparella et al (2023)[56] Italy	Quasi-experimental study	42 (29 adults, 13 children) 20.7 ± 8.6 AaO: 11.7 ± 7.7 years	Intensive rehabilitation (physiotherapy, occupational therapy, practical manual activities, psychological support, speech therapy)	3 weeks for children 4 weeks for adults	CL	Ataxia severity	**SARA:** (+)[c]	Pre- and postintervention, results for the whole cohort
						Ataxia severity and functional impairment	FARS total: (+)[c]	
						Manual dexterity and fine motor coordination	**9-HPT:** (D, ND) 0 ns	
Samardzic (2023)[128] Montenegro	Case report	1 26 AaO: 21	Multicomponent physical therapy with proprioceptive neuromuscular facilitation stabilization techniques, manual massage, occupational therapy	3 weeks of rehabilitation	CL	Ataxia severity	**SARA** total: (+) (− 4 points)	Pre- and postintervention
						Functional independence	FIM (locomotion): (+) (+2 points)	
Teixeira et al (2018)[129] Brazil	Case report	1 29 AaD: 17	Dance (contemporary dance, belly dance) and somatic education	8 months	PROM	Impact of educational dance	IAADE: (+) (in all skills: to get up, to sit, shifting feet, shifting the ground, sitting position, body image, joint mobility, movement rhythm, fluency movement)	Pre- and postintervention
Heart interventions								
Yoon et al (2012)[51] Canada	Case report	1 14 AaD: 11	Heart transplantation	20-month follow-up	CL	Ataxia severity and functional impairment	FARS: (−) (+97) (mainly upper limb coordination, upright stability/ambulation)	Pre- and postintervention

(Continues)

TABLE 2 *Continued*

Author (year), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Intervention details	Duration of intervention/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator, reported result
					PROM(QoL)	QoL	PedsQL total: (+) (+5) (subscale physical functioning +21, psychosocial −1)	
					IMG	Cardiac function	Echo (+)	
Ivak et al (2016)[52] Czech Republic	Case report	1 23 AaD: 16		6-month follow-up 1, 2, 3, 4, 5, 6, 7, 8 years	CL	Ataxia severity and functional impairment	FARS total: (+) (−86) FARS total: (+) (−28) FARS total: (−) (+58)	Preintervention and 6 months postintervention/before surgery vs. 8 years after 6 months after surgery vs. 8 years after
					IMG	Cardiac function	Echo: (+)	
McCormick et al (2017)[53] United States	Case report	3 Child, 37, 37 AaD: 12, 24, 34		19-, 5-, and 8-year follow-up	CL	Neurological function	Neurological function (−)	Pre- and postintervention
					IMG	Cardiac function	Echo (+)	
Valero et al (2022)[130] Spain	Case report	1 58 AaO: 33		2.5 months after transplant	CL	Neurological function	Neurological function stable	Pre- and postintervention
					IMG	Cardiac function	Echo stable	
Anderson et al (2016)[131] United States	Case report	1 Child AaD: 4	Septal myectomy	7-year follow-up	IMG	Cardiac function	Echo (+)	Pre- and postintervention
Hayiroglu et al (2025)[132] Turkey	Case report	1 31 n.i.	Catheter ablation	1-year follow-up	IMG	Cardiac function	Echo (+)	Pre- and postintervention
					CL		ECG (+)	
tDCS								
Naeije et al (2023)[70] Belgium	RCT	24 Median age, range: 32 (15–66) Median AaO, range: 17 (6–45)	Anodal cerebellar tDCS	1-week treatment	CL	Ataxia severity	**SARA:** (+)[c] anodal tDCS 0 ns in sham	Pre- and postintervention, within groups
						Cognitive and emotional changes (nonmotor cerebellar function)	CCAS-S: (+)[c] anodal tDCS 0 ns in sham	
Portaro et al (2019)[133] Italy	Case report	1 29 AaO: 10	Robotic gait training, with a virtual reality game (Lokomat Pro) + Cerebellar anodal tDCS	8-week follow-up	CL	Ataxia severity	**SARA** total: (+) (−4) (subscales: gait, stance, sitting, heel-shin slide)	Pre- and postintervention
					L	Cerebellar modulation of motor cortex	CBI: (+) (−18)	
Auditory problems								
Rance et al (2010)[63] Australia	Quasi-experimental study	10 24.80 ± 11.43[d] AaO: 10.10 ± 4.59[c]	Use of personal FM-listening devices (Phonak Inspiro FM-transmitter paired with bilateral ISense ear-level receivers)	6-week device trial	CL	Hearing assessment	ABR, frequency, AM detection (−) vs. healthy control	Pre- and postintervention
					PROM	Hearing with the hearing aid	APHAB (+) (+)[c] in communication, noise, reverberation scores	
Frewin et al (2013)[65] United Kingdom	Case report	1 41 AaD: 10	Bilateral cochlear implantation + Rehabilitation (audiobooks, auditory training materials)	2 months of implant use (right unilateral) 2 months—bilateral	CL	Speech discrimination performance	Unilateral and bilateral: BKB sentences (+)	Pre- and postintervention
					PROM(QoL)	QoL	Unilateral: EuroQol 0	
						QoL in cochlear implant users	Unilateral: NCIQ (+) (especially social domain)	

(Continues)

TABLE 2 *Continued*

Author (year), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Intervention details	Duration of intervention/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator, reported result
Occupational therapy								
Ciancarelli et al (2011)[54] Italy	Quasi-experimental study	10 26.9 ± 8.2 n.i.	Occupational therapy + Intensive conventional neuromotor rehabilitation program	12 months	CL	Independence in daily living	Barthel Index (+)[c]	Pre- and postintervention
						Physical performance	Physical performance test (−)[c]	
						Basic daily living independence	Katz Index (+)[c]	
						Cerebellar dysfunction	Klockgether Scale: 0 ns	
						Manual dexterity and fine motor coordination	**9-HPT:** 0 ns	
Zanona et al (2015)[134] Brazil	Case report	2 28, 36 AaD: 8, AaO: 12	Occupational therapy	5 months of therapy	CL	Functional independence	FIM: (+)	Pre- and postintervention
						Motor performance	Muscle strength: 0 Range of motion: 0	
Vibration								
Herrero et al (2011)[64] Spain	Quasi-experimental study	10 38.1 ± 10.5 AaD: 14.3 ± 6.4	Whole-body vibration (WBV)	3 weeks	L	Circulation in muscles	Blood flow velocity: (+)[c]	Pre- and postintervention
						Neuromuscular activity	EMG amplitude: (+)[c]	
					PROM	Exercise intensity	RPE: (+) by higher vibration	
Neuromuscular electrical stimulation								
McGarrell et al (2025)[135] United States	Case report	1 36 n.i.	Neuromuscular electrical stimulation (NMES)	1 month	L	Muscle endurance	EI: (+)	Pre- and postintervention
						Mitochondrial capacity	Mitochondrial capacity: 0	
						Muscle response to a single stimulus	Twitch contractions: (+)	
Scoliosis management								
Leighton et al (2013)[55] Canada	Case report	2 (twin sisters) 14 Early onset	Posterior spinal fusion	Follow-up: 2, 6, 25 weeks, 2 years	CL	Physical function	Standing alignment: (+) Pain: (+) Gait and endurance: (−) Stable sitting position: (+) Upper extremities function: 0	Pre- and postintervention
					PROM (S) C	Satisfaction	Satisfaction of patients and caregivers: (+)	
Speech therapy								
Batista and Conceição (2025)[136] Brasil, Australia	Case report	1 23 AaO: 23	Speech therapy (in-person) Expressiveness Development Program for Oral Communication	n.i.	CL	Speech assessment	Auditory-perceptual evaluation: Reading: (+) Absence of vocal deviation: (+) Adequate of vocal frequency: (+) adequate speech rate: (+)	Pre- and postintervention
					PROM (S)		Diction: 0 Sound of the voice: (+) Speaking experience: (+)	

(Continues)

TABLE 2 *Continued*

Author (year), country	Study design	Sample size (N)/Mean age ± SD (years)/FA characteristics[a]	Intervention details	Duration of intervention/ follow-up	Outcome type	Assessed feature/symptom	Outcome measure: result[b]	Comparator, reported result
Cognitive therapy								
Ciancarelli et al (2010)[67] Italy	Case series (case report)	24 32.48 ± 10.81 DD: 13.38 ± 7.98 years[d]	Cognitive therapy (modules and tasks to develop several skills, eg, memory, attention and concentration, language and literacy, visuospatial processing, daily life and functional skills, reading and writing)	6 days a week during three separate 3-week hospital stays 1-year follow-up	CL	Cognitive function	MMSE: 0 ns	Pre- and postintervention
						Long-term memory	The Rey 15-Item Memorization Test for long-term memory: 0 ns	
						Nonverbal reasoning/fluid intelligence	RCPM: 0 ns	
						Executive function and language	Phonemic Verbal Fluency Test: 0 ns	
						Processing speed and attention	SDMT: 0 ns	
						Short-term memory	Rey 15-Item Memorization test for short-term memory: (+)[c]	
						Cognitive flexibility and inhibition	Stroop Colour-Word Interference Task: (+)[c]	
					PROM	Depression symptoms	Zung SDS: 0 ns	

[a]FA characteristics: AaO, DD, DS, AaD, or YsD.
[b]Core outcome measures results: +, improvement; −, deterioration regardless of the treatment; 0, no effect.
[c]Significant effect.
[d]Mean (age at onset, disease duration) calculated from the available data in the publication.

Abbreviations: 9-HPT (D, ND), 9-Hole Peg Test (dominant, nondominant); AaD, age at diagnosis; AaO, age at onset; ABR, auditory brainstem response; AM, amplitude modulation; APHAB, abbreviated profile of hearing aid benefit; BBS, Berg Balance Scale; BKB, Sentences Bamford–Kowal–Bench Sentences; C, caregiver; CBI, Cerebellar Brain Inhibition; CCAS-S, Cerebellar Cognitive Affective Syndrome Scale; CL, clinical; DD, disease duration; DS, disease stage; ECG, electrocardiography; Echo, echocardiography; EI, endurance index; EMG, electromyography; EuroQol/EQ-5D (5 L), EuroQol 5-dimension (five-level) questionnaire; Friedreich's ataxia; FAIS, Friedreich Ataxia Impact Scale; FAIS ADL, Friedreich's Ataxia Impact Scale Activities of Daily Living; FARS, Friedreich Ataxia Rating Scale; FIM, Functional independence measure; IAADE, Instrumento de Avaliação da Aprendizagem na Dança Educacional (Monitoring Instrument Learning in Educational Dance); ICARS, International Cooperative Ataxia Rating Scale; IMG, imaging; L, laboratory; MMSE, Mini-Mental State Examination; NCIQ, Nijmegen Cochlear Implant Questionnaire; n.i., no information; ns, not significant; PedsQL, Pediatric Quality of Life Inventory; PGI-C, patient global impression–change; PROM, patient-reported outcome measure; QoL, quality of life; RCPM, Raven's coloured progressive matrices; RCT, randomized controlled trial; RPE, rate of perceived exertion; S, subjective; SARA, Scale for the Assessment and Rating of Ataxia; SD, standard deviation; SDMT, symbol digit modalities test; SF-36, Short Form Health Survey with 36 questions; tDCS, transcranial direct current stimulation; YsD, years since diagnosis; Zung SDS, Zung self-rating depression scale.

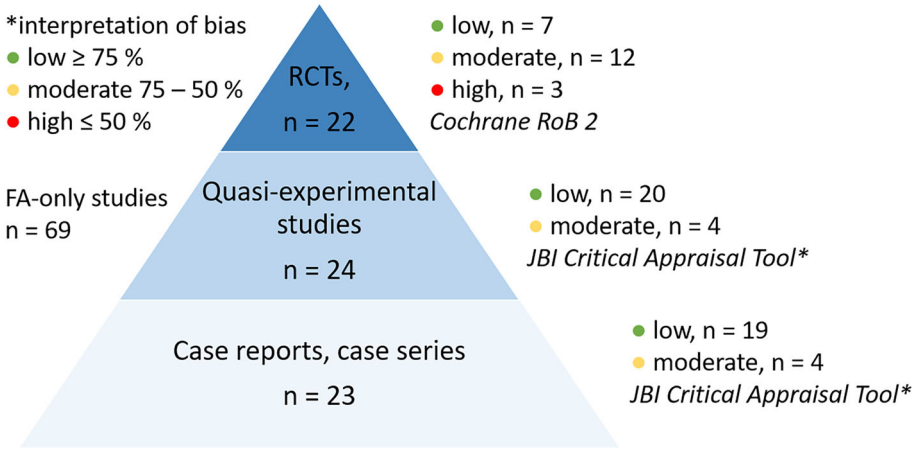


FIG. 2. Risk of bias assessment performed for all included studies (n = 69 for Friedreich's ataxia [FA] only) using certain tools depending on the study design. *The answers from JBI Critical Appraisal Tool have been standardized[29] and presented in the color manner. RCT, randomized controlled trial. [Color figure can be viewed at wileyonlinelibrary.com]

outcome measure in each study. Conversely, some nonpharmacological interventions also demonstrated deterioration in some outcomes, for example, neurological function after heart transplantation,[51-53] physical performance after the occupational therapy,[54] or gait and endurance after scoliosis surgery.[55]

When observing subgroups, nonpharmacological interventions tended to be more effective in ambulant, younger patients.[56]

The most common nonpharmacological interventions in studies with mixed ataxia patients were transcranial direct current stimulation (29.4%) and any rehabilitation (23.5%, including multimodal rehabilitation of 5.9%). In addition, other approaches were presented for mixed populations, such as video games (ie, training including body-controlled video games, often with the use of virtual reality) (17.7%) and noninvasive focal mechanical vibration-proprioceptive stabilizer (11.8%).

Alignment of Outcome Measures and Evidence Synthesis According to the ICHOM Criteria

Outcome Measures Used

A summary of outcome measures used across all interventions for FA-only studies is demonstrated in Fig 1G.

Mostly, clinical measures (CL) were used (60 studies in total; 87%), with SARA (24 studies) and FARS (19 studies; FARS Neuro [neurological examination from FARS] 2 studies, mFARS/mFARS Neuro [modified FARS] 9 studies) being the most prevalent measures for ataxia severity. Also, the 9-HPT (9-Hole Peg Test) was commonly used for manual dexterity and upper limb coordination (21 studies) and the T25FW (Timed 25-foot Walk) for mobility and gait assessments (12 studies) (Fig. 1H).

Laboratory measures (L) (25 studies; 36%) mainly included frataxin levels (16 studies), oxidative stress markers (2 studies), iron metabolism (2 studies), and various assessments of cerebellar function (1 study) or muscle function (2 studies). Imaging outcomes (IMG) (25 studies, 36%) included echocardiography (23 studies) imaging of the brain (white or gray matter) or spinal cord (2 studies).

Patient-reported outcome measures (PROMs) were included in only 37 studies (54%), whereas subjective patient perspectives were gathered in 7 studies (10%) and quality-of-life assessments in 18 studies (26%). The most commonly used PROM was the short form health survey with 36 questions (SF-36; 12 times), modified Fatigue impact scale (MFIS; 6 times), and self-reported assessment of ADL (5 times). Only four studies (6%) for FA-only patients included subjective caregiver perspective,[35,55,57,58] but no caregiver burden or well-being measures were used.

Administered outcome measures in mixed ataxia studies are demonstrated in Tables S3 and S4 and Figure S2.

Addressed Health Domains

Figure 3 categorizes the interventions for patients with FA into seven domains: physical health, overall health, social health, mental health, clinical status, caregiver support, and economic considerations. Each domain demonstrates the number of assessments in FA-only studies (n = 69 studies, n = 280 assessments in total), in which at least one of the earlier-mentioned outcomes was addressed. Identified studies most often addressed the physical health domain, with 118 assessments (42.3%) from 54 studies (78.3%). The predominant assessments were cardiac function (23 studies), upper limb and manual dexterity (21 studies), as well as mobility and gait

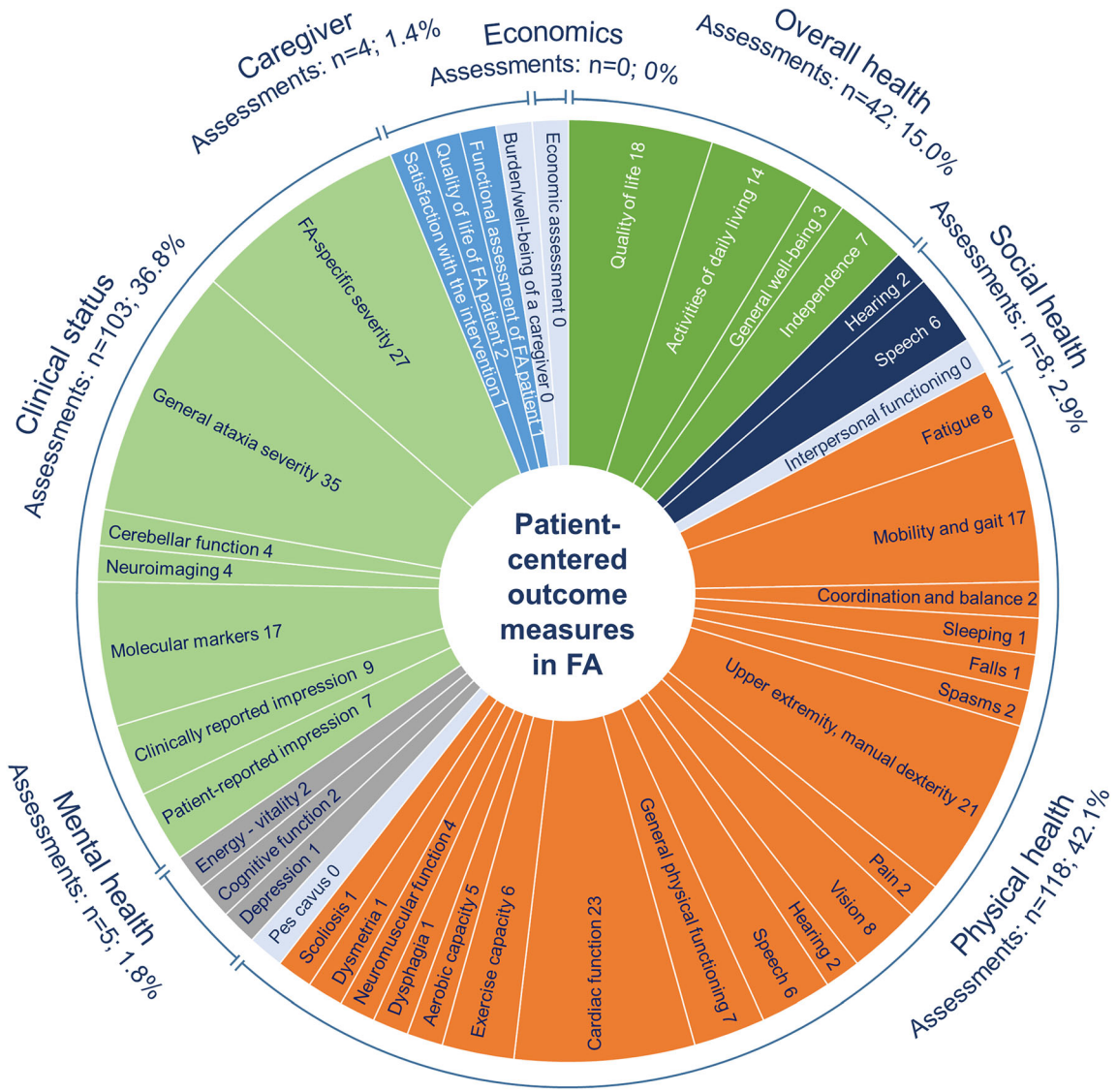


FIG. 3. Patient-centered outcome measures used in the included studies; n = 280 assessments from 69 studies for Friedreich's ataxia (FA)-only patients and the division in domains and subdomains. [Color figure can be viewed at wileyonlinelibrary.com]

(17 studies). The overall health domain encompassed aspects of health-related quality of life, which was the most prevalent assessment in this domain (18 studies), as well as ADL (14 studies) and independence (7 studies). Overall health was addressed in 42 assessments (15.1%) from 30 studies (43.5%). Clinical status was the second most commonly addressed domain, with 54 studies (78.3%) and 103 assessments (36.8%). Generic and FA-specific ataxia severity (35 and 27 studies, respectively) and molecular markers (17) were the most prevalent in this domain.

None of the interventions focused on the social health domain in terms of interpersonal functioning. However, hearing (two studies) and speech (six studies) were addressed, which are physical symptoms that directly influence interactions with other people. In total, social health was investigated in only 11.6% of studies (n = 8) (and 2.9% of assessments, n = 8). Mental health was one of the least addressed domains, with four studies (5.8%) and five assessments (1.8%). Although caregivers were involved in four assessments (1.4%) from four studies (5.8%) as proxy ratings, caregiver burden and well-being were never used. The economic domain—that is, healthcare service utilization, costs, and cost-effectiveness—was neglected in all of the included studies.

The main targets for patients with mixed ataxia are demonstrated in Figure S4 and Table S12.

Effectiveness of Intervention Across Health Domains

Most of the reported outcomes showed no differences, although several demonstrated positive effects,

but they were rarely significant. Case reports for most subdomains reported positive effects. Details about domains and the effectiveness of interventions, including study designs and assessments, are available in Table S11.

Even though the physical health domain was most frequently addressed, just 10 significant positive results were reported for the following subdomains: upper extremity and manual dexterity,[59] mobility and gait (in the child population),[45] speech,[46,60] cardiac function,[43,61] exercise capacity,[50,62] hearing,[63] and neuromuscular function.[64]

Included studies did not show a clear improvement in patients' quality of life (overall health domain). The improvement was obtained in specific subdomains, for example, vitality,[58] physical functioning,[49] health transition,[36] or social health.[65] Moreover, independence significantly improved in one study[54] and ADL in two studies.[48,66]

Symptoms important for social interactions were effectively addressed. Speech improved significantly after pharmacotherapy[46,60] and hearing problems after the use of hearing device and cochlear implantation.[63,65] Speech therapy was more often investigated in mixed ataxia studies.

Several aspects of mental health were addressed in cognitive therapy,[67] but with no significant positive effect, except for improvements in short-term memory, cognitive flexibility, and inhibition. There was no effect on depression. Conversely, significant improvements in cognitive function (measured by the Cerebellar Cognitive Affective Syndrome Scale [CCAS-S]) have been reported, as well as subjective improvements in energy levels and significant improvements in the vitality.[50,68]

Significant improvements in the generic ataxia scale SARA were reported in six studies,[39,50,56,61,69,70] in the FA-specific scale FARS in four studies,[57,60,71,72] and in the mFARS in four studies.[47,48,73,74]

The patient's impression of the disease reported two significant improvements.[45,66] Frataxin concentration was the most commonly investigated biomarker, with a significant positive effect reported four times.[44,57,58,75] In addition, reduced oxidative stress was reported once[84] or twice as a reduced ferritin level, leading also to a reduction in oxidative stress.[75,76] In neuroimaging, significant improvement in fractional anisotropy in white matter was reported, but with no correlation with SARA or FARS,[32] as well as a significant increase of gray matter volume in the pulvinar and posterior parietal cortex with a correlation with SARA.[77]

Discussion

This systematic review identified 90 intervention studies in FA (69 FA only and 21 mixed ataxia) and analyzed key interventions, as well as their effects and alignment with standardized outcome sets of patient-centered treatment and care. Most studies were small and varied in design and quality, ranging from case reports to RCTs. Overall, pharmacological interventions often showed mixed effects, with omaveloxolone demonstrating more consistent benefits. In contrast, non-pharmacological approaches, such as rehabilitation and particularly multidisciplinary programs, were more frequently reported to improve patient-relevant outcomes. However, the evidence was based primarily on small case series and potential biases. Subgroup analyses also demonstrated a tendency for better intervention effects in a younger population, groups at earlier stages of FA, with a higher likelihood of faster disease progression.

Clinical Management Guidelines for FA indicated that most intervention recommendations are based on very low levels of evidence, with only a few achieving moderate strength but strong recommendation.[78] Multimodal rehabilitation has the strongest support for neurological components and fatigue, whereas cardiac interventions (eg, transplantation or heart devices), with limited evidence, may be considered on an individual basis in patients with impaired cardiac function. In our review, (multimodal) rehabilitation and heart interventions were the most prevalent nonpharmacological interventions, highlighting the importance of these approaches. Heart and muscle function are interdependent because the heart supplies oxygen and nutrients essential for muscle performance, while muscle activity supports cardiovascular health. Although movement-related symptoms are often the most disruptive in everyday life in FA,[15,38,79] cardiac complications may be less apparent to patients yet represent a significant life-threatening risk[38]; therefore, it is crucial to address these issues. Presented findings highlight both the potential of specific therapies and the substantial gaps in the existing evidence base of interventional research in FA. Future research should focus on strengthening the evidence base for interventions in FA, with particular attention to their impact on patients' daily lives.

Nonpharmacological interventions were more patient and symptom oriented and more frequently reported positive outcomes because they typically target specific functional impairments. They may also involve more active engagement of patients; for example, physical activity can improve energy and motivation,[80] or social interaction may contribute to a better overall effect.[81] However, these findings should be interpreted with caution given the frequent use of case reports and quasi-experimental designs, which are associated with a higher risk of bias. Pharmacological interventions often aim either to stop or at least to slow the disease progression; therefore, the positive effect may not be directly visible. Although placebo effects in neurodegenerative ataxias may reach up to 32% showing improvement in at least one ataxia rating scale,[82] the successful blinding of the RCT may minimize the expectation-related bias.[54]

Many medications proved ineffective; some improved only certain outcomes. Clear evidence for effective disease-modifying therapies remains lacking. Current disease-modifying therapeutic strategies in FA aim to increase frataxin expression or replacement, improve mitochondrial function, reduce oxidative stress, modulate downstream metabolic pathways, and provide neuroprotection.[83] Targeting multiple pathogenic mechanisms may enable complementary or combination approaches and support the development of more individualized treatments. Several mixed effects were reported for pharmacological interventions, where laboratory or imaging outcomes were improved, with no effect on clinical measures or PROMs. This mismatch between biological signals and clinical benefit underscores the complexity of FA and may indicate that an intervention influences underlying biological processes without yet producing detectable clinical or patient-perceived benefits. Clinically meaningful changes in patient-relevant outcomes may evolve gradually, requiring longer treatment and observation periods to capture clinical improvements. Understanding the mechanisms underlying therapeutic effects is crucial for optimizing interventions, establishing causal pathways, and translating promising findings into effective clinical treatments. Future research should therefore integrate the variety of outcomes, including laboratory, clinical, and patient-reported outcomes, in a complementary manner,[84,85] to better capture the association between outcomes and the full spectrum of treatment effects, ensuring that advances translate into meaningful benefits for patients.

Idebenone was the most frequently investigated medication; however, the results were inconclusive. The clinical trial IONIA in the pediatric population showed that idebenone did not improve cardiac function,[33] whereas in the open-label extension, potential therapeutic benefit to stabilize the disease progression and to improve specific symptoms, for example, fine motor skills and speech, was shown.[42] So far, omaveloxolone in the MOXIe trial demonstrated more consistent positive effects in terms of neurological progression assessed with mFARS.[47,48] Short-term effects and the long-term slowing of the progression in comparison with natural progression (almost 3 years) were demonstrated.[86] Greater improvement was reported for the patients without pes cavus and those who started the treatment earlier, suggesting its efficacy at the less severe FA stages.[73] Future research should therefore prioritize identifying responsive populations and specific symptoms to support more personalized and effective therapeutic strategies.

Outcome measures were heterogeneous across studies in this review, with clinical scales being most common and PROMs less prevalent. PROMs were reported in just more than half of the FA-only studies, highlighting the need for possible greater patient involvement and the development of standardized, responsive measures.[87-89] Several recommendations have been made regarding outcome measures used in FA research (eg, core measure instruments, including clinical scales such as SARA, 9-HPT, T25FW, and mFARS[113,114]) to facilitate a comprehensive evaluation[119] and good comparability between studies. It is crucial to use standardized outcome measures and reporting, with consistent thresholds for clinical relevance. Although the minimal clinically important difference (MCID) is essential for determining whether observed changes are clinically meaningful, currently, no disease-specific MCID values are available for FA.[90] Standard outcome measures in FA should capture clinically meaningful aspects of the disease, including neurological function and disease progression, health-related quality of life, mental well-being, and patient perspective. Selection should prioritize validated, responsive measures that are relevant to patients and aligned with the specific objectives of the intervention. This will enable consistent reporting and a clearer overview of interventional outcomes, ultimately leading to improved development of new therapies.

Physical health was the most frequently addressed domain, which demonstrates that FA is primarily considered a movement disorder. Holistic care of patients with FA requires recognizing it as a multidimensional disease and addressing more health domains, for example, psychosocial health. FA considerably affects mental health, with literature reporting the prevalence of depression in FA up to 40%[91,92] or other emotional issues (eg, decreased motivation, feeling fearful about the future, social isolation).[14,15] Deterioration in cognitive functions (eg, in emotional processing, social cognition) and CCAS has also been reported.[13,93-95] In addition, a loss of ambulation or transition between mobility devices as the disease progresses may directly influence mental health.[96,97] Patients with FA are often stigmatized in social life because of symptoms of movement and speech impairments resembling alcohol or drug use, which may further exacerbate the social isolation and mental health issues.[98] Although the gathered evidence level is low, the Clinical Management Guidelines strongly recommend counseling or therapy in case of depression and anxiety, as well as lifestyle changes (such as exercise, diet, social activities) or pharmacotherapy.[78] This indicates that psychosocial health is important and should be addressed more thoroughly to gather further evidence. Future interventional studies should therefore expand beyond physical function to systematically address psychosocial and cognitive domains, ensuring a holistic and patient-centered approach.

In our review, we found no studies that considered caregivers' burden or the impact of the availability of a caregiver. The perspective of caregivers of patients with FA has been largely neglected but should be included in research and interventions. Caregivers play a central role in supporting individuals with FA, yet often experience substantial physical, emotional, social, and

financial burden, which can negatively affect their own health and caregiving capacity.[137] Supporting caregivers may therefore not only improve caregiver well-being but also indirectly enhance patient care.

FA is a tremendous economic and societal burden.[99-102] The economic and health resource outcomes in FA, including healthcare utilization, informal care, caregiver productivity losses, and adverse health events, constitute a gap in the current research that has only recently begun to be addressed.[103,104] Therefore, future interventional studies should also consider incorporating such outcomes to capture the full societal and economic impact of FA and to inform sustainable healthcare planning and policy. Given the complexity of FA, comprehensive evaluation, including clinical, patient-reported, caregiver, health, economic, and psychosocial outcomes, may yield the best results.

Limitations

Although the searching strategy was broad and included several interventions, we cannot ensure that all existing interventions were included in this review. Studies with various designs and small sample sizes have been included, exhibiting a low-to-moderate bias. These aspects may significantly impact the level of evidence supporting the presented outcomes and limit their robustness and generalizability.

Implications for Future Research

Future interventional studies should use multicenter and robust study designs that incorporate a variety of clinical, patient-reported, and health system–relevant end points. The literature has indicated that patients with FA are motivated to participate in studies, which could help facilitate the setup of larger studies.[105] However, common barriers include the ethical allocation to a placebo group, treatment side effects, and the logistics of travel and participation.[105] Innovative, remote, or app-based interventional designs might overcome these barriers by reducing patient burden, increasing accessibility, and enabling more flexible participation in FA trials.

Interventions implemented in mixed ataxia populations can be further investigated in FA-only populations to confirm efficacy and reduce heterogeneity across distinct disease entities. Several nonpharmacological interventions are currently ongoing that target various issues, for example, swallowing and respiratory function,[106] standing balance,[107] speech therapy involving behavioral intervention,[108] biofeedback therapy,[109] or NAD+ (Nicotinamide adenine dinucleotide (oxidized form)) and exercise.[110] Nonpharmacological interventions must be investigated using more robust trial designs because controlled designs are still underrepresented. Similarly, several ongoing clinical studies at various stages are investigating new medications for FA.[111] Omaveloxolone has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), since 2023 and 2024, respectively,[18,19] as the first FA disease-modifying treatment for patients aged 16 years and older. Recently, vatiquinone, another candidate drug for FA treatment, was evaluated by the FDA; however, further evidence is still needed to prove its efficacy.[112] All presented studies and protocols show that there is constant development in the research on interventions for FA management, and new approaches are being tested, providing hope for patients with FA to gain access to another new and effective therapy.

Conclusion

This review summarizes current research on pharmacological and nonpharmacological interventions in FA and highlights symptoms and health domains that remain underexplored. Pharmacological interventions as disease-modifying therapies targeting pathophysiology of FA have shown mostly limited benefits to date, with omaveloxolone exhibiting considerable effectiveness. Omaveloxolone, although not yet widely available, may potentially become part of standard care in the future. Nonpharmacological approaches showed promise in symptom-driven research. Research has focused primarily on physical symptoms affecting movement, whereas many comorbidities, psychosocial health, caregiver burden, well-being, and economic aspects remain poorly studied. These gaps underscore the urgent need for further research. Translating findings into effective therapies requires rigorous research and multidisciplinary approaches that integrate all relevant health domains and involve both patients and caregivers.

Author Roles: (1) Research Project: A. Design, B. Organization, C. Execution; (2) Manuscript Preparation: A. Drafting Initial Version, B. Editing Final Version.
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Acknowledgments: We acknowledge the use of Freevectormaps because the world contour used in Figure 1H was obtained from https://freevectormaps.com/world-maps/WRLD-EPS-01-0004?ref=atr. Open Access funding enabled and organized by Projekt DEAL.

Financial Disclosures and Conflicts of Interest: J.F. has received consultancy honoraria from Vico Therapeutics and Biogen. M.G.-E. has received honoraria from Biogen and travel support from Apario and the Ataxia Global Initiative. B.M. has received consultancy honoraria from Biogen, Lilly, and EuroQol. T.K. has received, within the last 24 months, consulting fees from Arrowhead, Bristol-Myers Squibb, and UCB. All funding is unrelated to this study. Author disclosures are available in the Supporting Information.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.