A Systematic Literature Review on the Efficacy of Pharmacological Interventions in Ataxia

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Gunjan Bisht[1], Gagandeep Kaur[1], Sumeet Attri[1], Pankaj Rai[1], Barinder Singh[2]

[1]Pharmacoevidence, Mohali, India, [2]Pharmacoevidence, London, UK

CONCLUSION

- Omaveloxolone and riluzole have demonstrated potential in reducing ataxia symptoms, with evidence suggesting their efficacy. While other interventions have shown some symptom reduction, the findings have not reached statistical significance, underscoring the need for further research to comprehensively assess their effectiveness and potential benefits

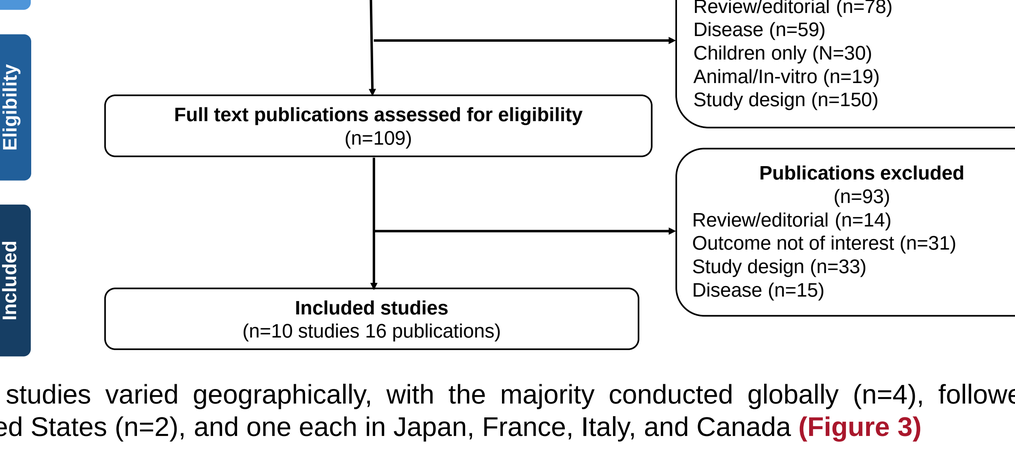
INTRODUCTION

- Ataxia is a condition characterized by a lack of coordination in voluntary movements, often linked to dysfunction of the cerebellum or sensory inputs like vestibular or proprioceptive pathways
- It is typically a symptom of underlying disorders, including infectious or immunologic causes, which may have limited treatment windows[1]
- While current therapies mainly focus on symptom management, there is a significant gap in treatments that address the underlying causes of ataxia
- This systematic literature review (SLR) aims to evaluate the efficacy of pharmacological interventions in ataxia

METHODS

- A systematic search was performed across key biomedical databases (EMBASE® and MEDLINE®) and trial registries from inception to May 2024 in accordance with Preferred reporting items for systematic reviews and meta-Analyses (PRISMA) guidelines, Cochrane Handbook and National Institute for Health and Care Excellence standard approach for conducting reviews. The prespecified eligibility criteria is presented in **Figure 1**
- Two independent reviewers reviewed each study, and a third reviewer resolved disagreements

Figure 1: Eligibility criteria for the systematic literature review



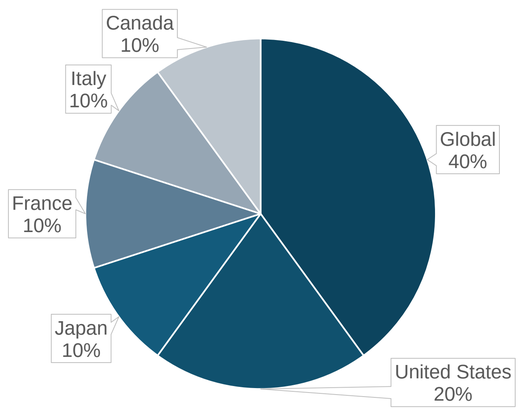
RESULTS

- Among the 449 publications identified, 10 studies evaluated the efficacy of pharmacological interventions in ataxia. A PRISMA diagram for selection of evidence is presented in **Figure 2**

Figure 2: Flow of studies through the systematic literature review

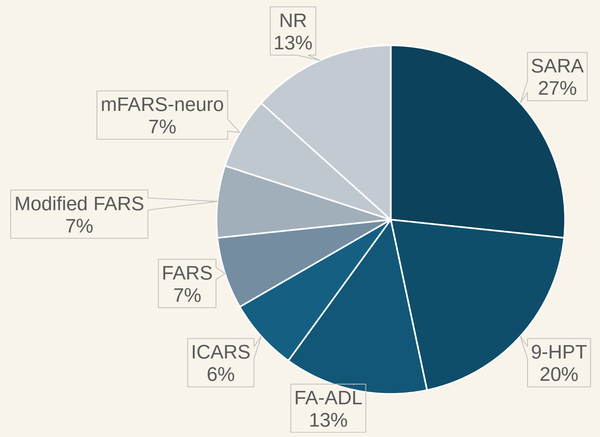
- The studies varied geographically, with the majority conducted globally (n=4), followed by the United States (n=2), and one each in Japan, France, Italy, and Canada **(Figure 3)**

Figure 3: Geographic distribution across the included studies



- The most used scales for efficacy assessment were the Scale for the Assessment and Rating of Ataxia (SARA, n=4), followed by the Nine-Hole Peg Test (9-HPT, n=3) and the Friedreich Ataxia-Validated Activities of Daily Living (FA-ADL, n=2). Other scales included the International Cooperative Ataxia Rating Scale (ICARS), Friedreich Ataxia Rating Scale (FARS), modified (m) FARS, and mFARS-neuro (n=1 each) **(Figure 4)**

Figure 4: Efficacy assessment scales used across the included studies



9-HPT: Nine-hole peg test, FA-ADL: Friedreich ataxia–validated Activities of Daily Living; FARS: Friedreich Ataxia Rating Scale, ICARS: International Cooperative Ataxia Rating Scale, NR: Not reported; SARA: Scale for the Assessment and Rating of Ataxia

- Four studies assessed the efficacy of rovatirelin, riluzole, and troriluzole using the SARA scale. At 12 months, a statistically significant improvement was observed with riluzole compared to placebo among patient with hereditary cerebellar ataxia (50% vs. 11%)
- Among remaining three studies with efficacy data using SARA scale, no significant differences were observed with rovatirelin, riluzole, and troriluzole versus placebo **(Table 1)**

Table 1: Summary of change in SARA scale scores across treatments in included studies

Study name	Treatment	Dose	Time point	CFB	p value
Nishizawa 2020	Rovatirelin	1.6 mg	24 weeks	-0.90	0.490
	Rovatirelin	2.4 mg	24 weeks	-1.23	0.058
	Placebo	-	24 weeks	-1.25	--
	Rovatirelin	1.6 mg	End-point	-0.75	0.176
	Rovatirelin	2.4 mg	End-point	-1.22	0.814
	Placebo	--	End-point	-1.15	--
	Rovatirelin	2.4 mg	24 weeks	-1.46	0.303
	Placebo	--	24 weeks	-1.13	-
	Rovatirelin	2.4 mg	End-point	-1.45	0.194
	Placebo	--	End-point	-1.05	--
Coarelli 2022	Riluzole	50 mg	1 year*	0.5	0.70
	Placebo	-	1 year*	0.3	--
NCT02960893	Troriluzole	140 mg	8 weeks	-0.81	--
	Placebo	--	8 weeks	-1.06	--

Mean value was reported; * Data reported for Median; CFB: Change from baseline

- Three studies assessed omaveloxolone, deferiprone, and luvadaxistat using the 9-HPT scale. At 48 weeks, omaveloxolone showed significant improvements in symptoms of friedreich's ataxia, with better mean change from baseline in 9-HPT scores (−0.0014 vs. −0.0001) **(Table 2)**
- On the other hand, the remaining two studies with efficacy data using 9-HPT scale showed no significant improvements with deferiprone and luvadaxistat compared to placebo **(Table 2)**

Table 2: Summary of mean change from baseline in 9-HPT scale scores for treatments across included studies

Study name	Treatment	Dose	Time point	CFB	p value
Pandolfo 2014	Deferiprone	20 mg/kg/d	6 months	0.0007	0.463
	Deferiprone	40 mg/kg/d	6 months	0.0005	0.453
	Placebo	--	6 months	-0.0008	--
Wang 2021	Luvadaxistat	75 mg	12 weeks	-0.00031	NS
	Luvadaxistat	300 mg	12 weeks	-0.00059	NS
	Placebo	--	12 weeks	0.00029	--
Lynch 2023	Omaveloxolone	150 mg	48 weeks	-0.0014	0.04
	Placebo	--	48 weeks	-0.0001	0.82

CFB: Change from baseline

- Two studies used FA-ADL scale to assess efficacy of omaveloxolone and luvadaxistat versus placebo; at 48 weeks, omaveloxolone showed significant improvements in symptoms of friedreich's ataxia using FA-ADL scale (−0.17 vs. 1.14) while no statistically significant difference in FA-ADL scores were observed between luvadaxistat and placebo **(Table 3)**
- Omaveloxolone also showed improvements in mFARS scores (47% vs. 27%) compared to placebo

Table 3: Summary of mean change from baseline in FA-ADL scores for different treatments in included studies

Study name	Treatment	Dose	Time point	CFB	p value
Lynch 2023	Omaveloxolone	150 mg	48 weeks	-0.17	0.042
	Placebo	--	48 weeks	1.14	--
Wang 2021	Luvadaxistat	75 mg	12 weeks	-0.29	NS
	Luvadaxistat	300 mg	12 weeks	-0.52	NS
	Placebo	--	12 weeks	-0.40	NS

CFB: Change from baseline

- Two studies evaluated idebenone and luvadaxistat showed only minimal improvements in ICARS, FARS, and mFARS-neuro compared to placebo **(Table 4)**

Table 4: Summary of mean change from baseline in different scale score across treatments in included studies

Study name	Treatment	Dose	Time point	Scale	Score
NCT00905268	Idebenone	180-360 mg/d	52 weeks	ICARS	1.6
	Idebenone	450-900 mg/d	52 weeks	ICARS	1.7
	Idebenone	1350-2250 mg/d	52 weeks	ICARS	1.2
	Placebo	--	52 weeks	ICARS	1.1
	Idebenone	180-360 mg/d	52 weeks	FARS	0.9
	Idebenone	450-900 mg/d	52 weeks	FARS	1.2
	Idebenone	1350-2250 mg/d	52 weeks	FARS	1.4
	Placebo	--	52 weeks	FARS	0.9
Wang 2021	Luvadaxistat	75 mg	12 weeks	mFARS-neuro	-1
	Luvadaxistat	300 mg	12 weeks	mFARS-neuro	-1.43
	Placebo	--	12 weeks	mFARS-neuro	-2.95

FARS: Friedreich Ataxia Rating Scale, ICARS: International Cooperative Ataxia Rating Scale, m-FARS: Modified FARS, SARA: Scale for the Assessment and Rating of Ataxia

- Treatment with amantadine hydrochloride found no improvement in lower limb function, but reported a 20% improvement in upper limb ataxia ($p < 0.05$)

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Disclosures

GB, BS, PR, SA, and GK, the authors, declare that they have no conflict of interest