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Novel therapeutic approaches in inherited neuropathies: A systematic Review

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Introduction

Management of inherited neuropathies relies mostly on **symptomatic** treatments.
In recent years, interventional trials have been conducted to develop disease modifying treatments.
The **aim** of this study was to systematically review **the therapies that have emerged in this field over the last five years.**

Methods

1) Compilation of List of Inherited Neuropathies

France Paris-Saclay

UK PanelApp

USA MayoClinic

List of genes merged from 3 panels

Extension of **the list** based on the expertise of the authors and **two experts** + crossing with existing **published data** (1,2,3,4).

2) Literature and Clinical Trial Database Searches

- Population: Human patients diagnosed with a disease from the list
- Intervention: Pharmacological treatment or diet
- Outcome: Clinical, Biological, Electro-physiological

Additional criteria:
- Original, full-text articles about interventional studies published in English after 1 January 2018.
- Retrospective observational studies were not included.
- Relevant articles were extracted from the reference sections of systematic or expert reviews and meta-analyses (Figure 1).

Figure 1. PRISMA flowchart of studies identified as relevant to the treatment of inherited neuropathies.

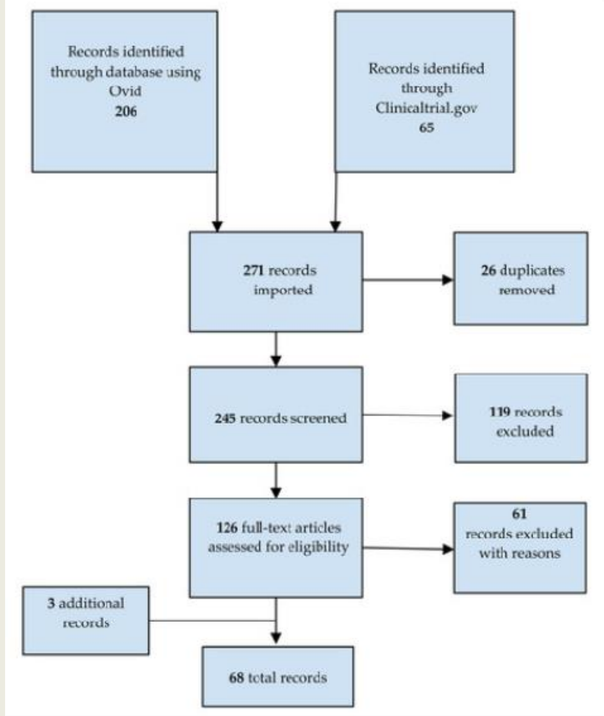

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flow diagram were followed for the design and reporting of this work.

Results

68 Total records

28 assessed neuropathy as a primary or secondary endpoint

40 did not assessed neuropathy as a primary or secondary endpoint…but

1) Approved disease-modifying drugs with positive impacts on neuropathies

Condition	Compound *Dose & administration*	Mechanism of action	Clinical trial identification	Current status
Hereditary transthyretin amyloidosis polyneuropathy (ATTRv-PN)	**Tafamidis** *20 mg, 1x/day, Orally*	TTR stabilizer	NCT00925002 (phase 3 LTE), NCT00409175 (phase 1/2), NCT00630864 (phase 2).	-EMA approval in 2011 for patients with stage 1 polyneuropathy (brand name VYNDAQEL, Pfizer). -Not approved by FDA for ATTRv-PN but approval was granted in 2019 for use at a higher dose in ATTR-associated cardiomyopathy.
	Patisiran *0.3 mg/kg 1x/3 weeks, IV*	siRNA targeting *TTR* mRNA	NCT01960348 (phase 3; APOLLO), NCT01961921 (phase 2 OLE), NCT03862807 (phase 3b).	-FDA approval in 2018 for ATTRv-PN of any stage and EMA approval in 2018 for the treatment of ATTRv-PN in adults with stage 1 or 2 polyneuropathy (brand name Onpattro, Alnylam Pharmaceuticals).
	Vutrisiran *25 mg, 1x/3 months, SC*	siRNA targeting *TTR* mRNA	NCT03759379 (phase 3; HELIOS-A study)	-FDA approval in 2022 for adult patients with ATTRv-PN and EMA approval in 2022 for adult patients with stage 1 or stage 2 polyneuropathy (brand name Amvuttra, Alnylam Pharmaceuticals).
	Inotersen *300 mg 1x/week, SC*	Antisense oligonucleotide targeting *TTR* mRNA	NCT01737398 (phase 3; NEURO-TTR), NCT02175004 (phase 3 OLE)	-FDA approval in 2018 for ATTRv-PN of any stage, and EMA approval in 2018 for patients with stage 1 or 2 polyneuropathy (brand name Tegsedi, Akcea Therapeutics)
Metachromatic Leuko-dystrophy (MLD)	**Atidarsagene autotemcel (arsa-cel)/HSPC-GT** *1 delivery*	Gene therapy	NCT01560182 (phase 1/2)	-Approved by EMA in 2020 and in the UK in 2021 (brand name Libmeldy, Orchard Therapeutics). -Under investigation in the USA. -Ongoing study in the late-juvenile variant of MLD (NCT04283227)

2) Promising trials that warrant further investigations

Condition	Compound *Dose & administration*	Mechanism of action	Clinical trial identification	Results	Current status
Spinocerebellar ataxia type 38 (SCA 38)	**Docosahexaenoic acid** *600 mg/day, Orally*	Replenish low levels of serum docosahexaenoic acid (DHA) caused by ELOVL5 gene mutation	NCT03109626	-Significant reduction (i.e., improvement) in SARA score and ICARS score. -Slight but not significant increase in total serum DHA compared to baseline. -Motor and sensory conduction velocities did not significantly worsen.	Further investigations needed.
Hereditary sensory and autonomic neuropathy (HSAN1)	**L-serine** *400 mg/kg/day, Orally*	Provides normal substrate of enzyme serine palmitoyltransferase	NCT01733407 (phase 1/2)	-Quantitative improvement in the CMTNS. -1-deoxySL levels declined significantly. -Significant change at 1 year in epidermal nerve fibre density at distal site. -No treatment effects were detected in nerve conduction studies.	Further investigations needed.
Charcot–Marie–Tooth 1A (CMT1A)	**Combination of baclofen, naltrexone and sorbitol/PXT3003** *5 mL, 2x/day, Orally*	Downregulation of PMP22 overexpression	NCT02579759 (phase 3)	-Significant improvement in the ONLS score and 10MWT. -No statistically significant change in nerve conduction studies.	Open-label continuation study (NCT03023540) ongoing.
Metachromatic Leuko-dystrophy (MLD)	**rhASA/HGT-1110** *10, 30, or 100 mg or 100 mg manufactured using a revised process, EOW, Intrathecal*	Enzyme replacement therapy	NCT01510028 (phase 1)	-Tendency towards a less pronounced decline in GMFM-88 score in patients receiving 100 mg than in the other cohorts. -CSF sulfatide and lysosulfatide levels fell to within normal ranges in both 100 mg cohorts. -Stable nerve function.	Extension study (HGT-MLD-071; NCT01887938) ongoing.

Discussion

- Several therapeutics were demonstrated to cause **changes in biomarkers thought to be causal of neuropathies** and should be tested with a focus on neuropathy in further trials.
  - ❖ NTLA-2001, Tolcapone and Eplontersen for patients with ATTRv-PN,
  - ❖ Givosiran for patients with Acute Intermittent Porphyria,
  - ❖ ERT, EET, and SRT for patients with Fabry disease.
- **Improvements in neurological assessments** were observed with some drugs but further investigations are needed in terms of efficacy on neuropathy.
  - ❖ EPI-743, RT001 and Omaveloxolone for patients with Friedreich ataxia, especially since Omaveloxolone has recently been approved by the FDA.
  - ❖ Leriglitazone for patients with X-linked Adrenoleukodystrophy.
  - ❖ Intra-Erythrocyte Dexamethasone Sodium Phosphate for patients with Ataxia-Telangiectasia.

Added value of this analysis

- The list provided here **includes genes not described in recent publications** and highlights the **inconsistencies** among published data and the different gene panels used for this analysis.
- Most clinical trials have been conducted with subjects diagnosed with **complex disorders** that may present peripheral neuropathy as a clinical component rather than pure hereditary neuropathies. In this context, **less than 50% of the studies assessed neuropathy** as a primary or secondary outcome.
- **Nine additional therapies** were identified that were not included in the systematic review published by Jennings et al. in 2021 [5], attesting to the **increased interest** in this field over recent years.
- Among the studies that assessed neuropathy, **various scales or biomarkers** were used, preventing a comparison between studies. Moreover, scoring systems validated for use in evaluation of the progression of neuropathy, **may not be appropriate** in all circumstances, are **subjective** and **cannot reliably detect subtle changes** especially in small cohorts.
- It will be critical to **develop objective and reliable methods** for this analysis. Research is ongoing to evaluate disease progression in subjects with peripheral neuropathies, including the use of wearable technologies [6,7], nerve sonography [8], intramuscular fat accumulation demonstrated by MRI imaging of the lower limbs [9], elevated plasma neurofilaments light chain concentration [10], and changes in the motor unit index (MUNIX) (NCT03715283).

Limitations of this analysis

- Our search was limited to studies with results **published after 1 January 2018.** For this reason, several clinically validated therapies for inherited neuropathies (e.g., vitamin E for Ataxia with vitamin E deficiency, riboflavin for Brown–Vialetto–Van–Laere, diet to limit pristanic acid for Refsum disease, etc.) were not captured in our search (but are well described by Fernandez-Eulate et al. [1]), nor were unsuccessful trials prior to 2018 (e.g., ascorbic acid, progesterone antagonists/modulators in CMT1A).
- Similarly, **suspended studies** (e.g., the gene therapy scAAV1.tMCK.NTF3 for CMT1A; NCT03520751) **were not considered**.
- Finally, we **did not include preclinical studies or recruiting trials**, thereby missing potential future therapeutic approaches (e.g., gene therapies for Charcot–Marie–Tooth type 4J and X, AT007 for sorbitol dehydrogenase deficiency patients).

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Abbreviations

TTR, transthyretin; EMA, European Medicines Agency; FDA, US Food and Drug Administration; **IV, Intravenously; siRNA,** small interfering RNA; OLE, open-label extension; **SC, subcutaneously;** SARA, Scale for the Assessment and Rating of Ataxia; ICARS, International Cooperative Ataxia Rating Scale; ONLS, Overall Neuropathy Limitations Scale; 10MWT, 10 m walk test; EOW, every other week; ERT, enzyme replacement therapy; EET, enzyme enhancement therapy; SRT, substrate reduction therapy;

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