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Targeted therapies for hereditary peripheral neuropathies: Systematic review and steps towards a 'treatabolome'

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Hereditary peripheral neuropathies are inherited disorders affecting the peripheral nervous system, including Charcot-Marie-Tooth disease, familial amyloid polyneuropathy and hereditary sensory and motor neuropathies. While the molecular basis of hereditary peripheral neuropathies has been extensively researched, interventional trials of pharmacological therapies are lacking. We collated evidence for the effectiveness of pharmacological and gene-based treatments for hereditary peripheral neuropathies. We searched several databases for randomised controlled trials (RCT), observational studies and case reports of therapies in hereditary peripheral neuropathies. Two investigators extracted and analysed the data independently, assessing study quality using the Oxford Centre for Evidence Based Medicine 2011 Levels of Evidence in conjunction with the Jadad scale. Of the 2046 studies initially identified, 119 trials met our inclusion criteria, of which only 36 were carried over into our final analysis. Ascorbic acid was shown to have no therapeutic benefit in CMT1A, while a combination of baclofen, naltrexone and sorbitol (PXT3003) demonstrated some efficacy, but phase III data are incomplete. In TTR-related amyloid polyneuropathy tafamidis, patisiran, inotersen and revusiran showed significant benefit in high quality RCTs. Smaller studies showed the efficacy of L-serine for *SPTLC1*-related hereditary sensory neuropathy, riboflavin for Brown-Vialetto-Van Laere syndrome (*SLC52A2/3*) and phytanic acid-poor diet in Refsum disease (*PHYH*). The 'treatable' variants highlighted in this project will be flagged in the treatabolome database to alert clinicians at the time of the diagnosis and enable timely treatment of patients with hereditary peripheral neuropathies.