ADVANCES IN DIAGNOSIS AND MANAGEMENT OF DISTAL SENSORY POLYNEUROPATHIES

Matthew Silsby[1,2], Eva L. Feldman[3], Richard D. Dortch[4,5], Alison Roth[4], Simon Haroutounian[6], Yusuf A. Rajabally[7], Steve Vucic[2], Michael E. Shy[8], Anne Louise Oaklander[9], Neil G. Simon[10]

Affiliations:

1. Department of Neurology, Westmead Hospital, Sydney, Australia
2. Brain and Nerve Research Centre, Concord Clinical School, Sydney Medical School, The University of Sydney, Sydney, Australia
3. Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA
4. Division of Neuroimaging Research, Barrow Neurological Institute, Phoenix, Arizona, USA.
5. Vanderbilt University Institute of Imaging Science, Department of Radiology and Radiological Sciences, Department of Biomedical Engineering; Vanderbilt University, Nashville, Tennessee, USA.
6. Department of Anesthesiology, Washington University School of Medicine, St Louis, Missouri, USA
7. Inflammatory Neuropathy Clinic, Department of Neurology, University Hospitals Birmingham; Aston Medical School, Aston University, Birmingham, UK.
8. Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA
9. Nerve Unit, Departments of Neurology and Pathology (Neuropathology), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
10. Northern Beaches Clinical School, Macquarie University, Northern Beaches Hospital, Sydney Australia

Running Title: Advances in DSP

Word count (excl Abstract): 6384

Abstract word count: *150*

Tables: 2

Figures: 3

References: 111

Corresponding author:

Prof. Neil Simon

Northern Beaches Clinical School, Macquarie University

Northern Beaches Hospital

Suite 6A, 105 Frenchs Forest Rd W

Frenchs Forest NSW 2086 AUSTRALIA

F: +61 2 9981 7880

T: +61 2 9982 2270

E: neil@nbneuro.com.au

Abstract

Distal sensory polyneuropathy (DSP) is characterized by length-dependent, sensory-predominant symptoms and signs including potentially disabling symmetric chronic pain, tingling, and poor balance. Some patients also have or develop dysautonomia or motor involvement depending on whether large myelinated or small fibers are predominantly affected. Although highly prevalent, diagnosis and management can be challenging. While diabetes and classic toxic causes are well-recognized, there are increasingly diverse associations, including with dysimmune, rheumatological, and neurodegenerative conditions. Approximately half of cases are initially diagnosed as idiopathic despite thorough evaluation, but often, the causes emerge later as new symptoms emerge or testing advances, for instance with genetic approaches. Improving and standardizing DSP metrics, as done earlier for motor neuropathies, would permit in-clinic longitudinal tracking of natural history and treatment effects. Standardizing phenotyping could advance research and permit trials of potential therapies, which lag so far. This review updates on recent advances and summarizes current evidence for specific treatments.

Introduction

Peripheral polyneuropathy is among the most common neurological conditions, affecting approximately 4% of the population,[1] and prevalence increases significantly with age.[2] Distal sensory polyneuropathy (DSP) accounts for most peripheral polyneuropathy presentations,[3] which are clinically categorized into isolated small fiber neuropathies (SFN), isolated large fiber neuropathies (LFN), or mixed fiber neuropathies (MFN) with overlapping small and large fiber involvement. Accurately diagnosing DSP and the underlying etiology is crucial for appropriately managing the patient and their symptoms. This review covers a broad subject and is therefore deliberately selective rather than systematic. It will briefly review the typical clinical presentations and common causes of DSP, with more expansive coverage of new and emerging conditions and their suspected pathophysiology. Additionally, diagnostic techniques to expedite diagnosis will be discussed, with a focus on newer modalities. Lastly, current available treatment and potential future directions for managing DSP will be explored.

Clinical Features

According to the 2020 consensus case definition of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) group, DSP presents with symmetrical, length-dependent, abnormalities in one or more sensory modalities (e.g., vibration perception) in the absence of muscle weakness.[3] Diagnoses are made by clinically assessing these modalities (e.g., tuning-fork vibration thresholds). The 2020 diagnostic criteria for idiopathic DSP include a framework for diagnosing and differentiating its subtypes, which this review utilizes.[3] "Definite" diagnoses require ≥1 sensory symptom, ≥1 sensory exam abnormality/sign, and no muscle weakness, for at least three months' duration (Box 1). Mixed fiber neuropathy diagnoses require small fiber plus

large fiber neuropathy features (Figure 1). In most cases of sensory-predominant neuropathies, symptoms begin in the distal-most extremity consistent with axonopathy, but a proportion have non-length dependent asymmetric onset, with early ataxia. The latter pattern indicates dysfunction in the more proximal dorsal root ganglion cell bodies.[4] This may be dysimmune, post-infectious, toxic, or paraneoplastic,[5] and will not be discussed further other than to say evaluation should be rapid as many patients require immunotherapy and thorough investigation for malignancy, which should also include repeated assessment over years to exclude subsequent development of previously undetectable neoplasm.

Update on etiologies

Virtually any condition that degrades the general internal or nerve-specific environment stresses distal axons. These are vulnerable to interruptions of supply of nutrients and macromolecules from their far-distant cell bodies. The traditional view of single causes of neuropathy is yielding to a more nuanced view that distal nerve health is a dynamic equilibrium between multiple positive and negative influences, some of which can be modified. Risks for DSP vary in different populations and environments. Of note, environmental causes including smoking and air pollution have been underappreciated. The most prevalent cause of DSP worldwide is diabetes mellitus, which is responsible for one quarter to one half of cases.[6] DSP has many etiologies, including toxic exposures, autoimmune or inflammatory conditions, infections or their immune sequelae, malignancy including paraneoplastic phenomena, nutritional deficiencies or excesses, and hereditary causes (Table 1).

Metabolic

The development t of DSP in type 1 and type 2 diabetes was initially thought to be purely due to hyperglycemia.[7] However, tight glycemic control only prevents or slows DSP onset and progression in patients with type 1 diabetes[8] indicating additional risk factors in type 2 diabetes. Increasingly, studies support a broader association between the metabolic syndrome and DSP. A recent study of obese (n=102) versus lean (n=53) participants stratified by glycemic status confirmed contributions of obesity and prediabetes on development of DSP, independent of and in addition to type 2 diabetes.[9] Further studies associate other metabolic syndrome components as neuropathy risks, including triglycerides and high-density lipoprotein cholesterol.[10] The Look AHEAD study found that extent of weight loss correlated with significant decreases in DSP.[11] Thus, obesity and components of the metabolic syndrome, as well as their comorbidities, may have larger roles in DSP development than previously appreciated.

Potential pathophysiological mechanisms and therapeutic implications

The underlying pathophysiology of DSP may be distinct in type 1 and type 2 diabetics. In both instances, excess energy substrates interfere with mitochondrial bioenergetics and induce oxidative stress and an inflammatory milieu (Figure 2). Well-coordinated mitochondrial dynamics are essential to maintain the massive energy requirements of the distal axon for both the resting state and for signal transduction. In fact, the failure of mitochondria to traffic to distal areas of long axons mirrors the stocking-glove pattern of DSP. *In vitro* investigations in dorsal root ganglia demonstrate that excess long-chain saturated fatty acids impair trafficking and depolarizes membranes of mitochondria,[12] effects absent in conditions of excess glucose or short-chain unsaturated fatty acids.[13] *In vivo*, a high-fat diet rich in long-chain saturated fatty acids similarly depolarizes axonal mitochondria and

impairs sensory neurons' ability to send potentials at physiological frequencies.[14] Overall, dysfunctional mitochondria induce energy shortages and neuronal injury.

Hyperglycemia has well-documented impacts on increased advanced glycation end products, polyol and hexosamine metabolism, and protein kinase C signaling trigger inflammatory responses and change axon electrophysiology.[15] Low-grade inflammation and oxidative stress increase levels of methylglyoxal, which correlates with the development of DSP,[16] and modifies the transient receptor potential cation channel, subfamily A, member 1, leading to hyperalgesia.[17] Animal studies also suggest possible mechanisms through liver X receptor (LXR) signaling and its relationship to NADPH oxidase 4 (Nox4).[18] Genome-wide association studies are also contributing new candidates, for instance *SLC25A3* related to mitochondrial oxidative phosphorylation.[19] Additionally, mutations, changes in expression levels, and posttranslational modifications to voltage-gated sodium channels, voltage-gated potassium channels, and ligand-gated transduction channels may confer higher risk of developing neuropathic pain.[15] We expect that investigations of ion channels, genome-wide association studies for genetic variants linked to painful DSP, and deeper understanding of pain pathways will suggest rational, mechanism-based therapeutic strategies for pain control.

Large, randomized trials of lifestyle interventions are lacking, but the American Diabetes Association now recommends exercise and diet for patients with type 2 diabetes as a first-line intervention for DSP.[20] Although high-fat diets in mice alter the sciatic nerve lipidome and expression of the enzyme required for triglyceride synthesis,[21] these changes are reversible upon dieting, advocating for this lifestyle change in humans. Monounsaturated fatty acids may better support mitochondrial trafficking and membrane potential.[22] Many experts recommend encouraging exercise, healthy diet, and weight control for all DSP patients to maximize nerve health and resilience.

Statins and DSP

This reported association remains controversial at present, despite cross-sectional observational studies and case reports suggesting potential links between development of neuropathy and exposure to statin therapy. A confounder of these studies is that treatment groups were typically prescribed statin because of metabolic or vascular risk factors, whereas comparison groups consisted of healthy controls not taking statin. As above, between-group metabolic profiles differences may in fact have played a larger role in prevalence of neuropathy. A 2020 study queried the Danish national healthcare registry to identify all patients with incident type 2 diabetes during a 15-year period. It reported no difference in the incidence of neuropathy between statin users and non-users, though there was a potential signal of increased risk within the first year of therapy in new users (hazard ratio 1.31, 95% CI 1.12-1.53).[23] This was not present after two years of follow up, and is argued by the authors to be outweighed by the benefits that statin therapy confers in improving cardiovascular health.

Dysimmune and Inflammatory

The association between autoimmunity and sensory neuropathy is well-described, particularly in Sjogren's disease.[24] The discovery of antisulfatide antibodies 20 years ago was associated with various neuropathy presentations including DSP,[25] although more recent scrutiny questions the pathological relevance of these antibodies, as one study showed the majority of their cohort had concurrent anti-MAG antibodies.[26] Whether other newly described antibodies have causal pathogenic roles or are merely bystanders or indirect evidence of disturbed immunity also requires further investigation and is a current area of active research. Nevertheless, ongoing discovery of autoantibodies may help to direct care of patients initially considered idiopathic, and therefore left untreated, towards potential therapies. This is

particularly evident in acquired demyelinating neuropathies, which has unlocked access to secondary targeted therapies. A potential advantage in future clinical trials is that incompletely characterized dysimmune neuropathies appear to respond to the same immunotherapies used for better-defined dysimmune neuropathies; however, determining true responses can be confounded by strong placebo effects and monophasic or waxing/waning courses that improve spontaneously over time. A current central problem, too, is how to manage patients with strong but indirect evidence of a dysimmune etiology; for example, blood markers of dysimmunity and/or other dysimmune diagnoses, yet not having identified autoantibodies, given that many or most remain undiscovered. Furthermore, little is known about the contributions of T cells and anti-idiotype antibodies, which are under studied areas of research.

Small fiber neuropathies

Although knowledge is incomplete, most of the clinical studies, and a few small studies using patient sera to passively transfer SFN into animals,[27] increasingly suggest that a substantial portion of initially idiopathic SFN may involve dysimmunity and inflammation, implying potential roles for immunomodulatory therapies.[28] Trisulfated heparin disaccharide (TS-HDS) antibodies have been reported in as many as 37% of patients with idiopathic SFN,[29] antiplexin D1 antibodies in 12.7% of patients,[30] and antibodies against the fibroblast growth factor receptor 3 (FGFR3) in up to 15%.[31] However, it should be noted that a recent placebo-controlled study of IVIg in SFN with TS-HDS and FGFR-3 autoantibodies found no significant improvement in nerve fiber density on skin biopsy or in neuropathy clinical scores, potentially calling into question their role in pathogenesis.[32] Importantly, this was a pilot study and larger trials are needed.

A 2022 study of 58 SFN patients and 20 matched healthy controls screened their sera for over 1600 immune related antigens, reporting associations with three novel autoantibodies; anti-MX1, anti-DBNL, and anti-KRT8.[33] Regarding whether or not identified antibodies are pathogenic, a small series of 7 patients with anti-FGFR3 antibodies found elevated prevalence (3) of SFN illnesses, one acute demyelinating neuropathy and one sensorimotor polyneuropathy.[34] Although antibody titers varied over time, in some cases disappearing,[34] bringing uncertainty about clinical relevance, dysimmune conditions often include T-cell mediated inflammation and cell damage that lingers even after pathogenic antibodies subside, particularly if these were triggered by infections. Axonal regeneration is often incomplete and includes mistargeting, so uncoupling of antibody titers from clinical symptoms does not necessarily exclude immune causality.

Large fiber neuropathies

The acute and chronic forms of large-fiber DSP have been far better studied, given near universal availability of nerve condition studies. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a dysimmune LFN that involves sensory, motor, autonomic and sensory small fibers to varying extents, including pure or predominant sensory subtypes.[35] Sensory CIDP is identified through exclusively distally impaired vibration and proprioception, with consequent sensory ataxia and areflexia. The distal form of CIDP, previously labelled distal acquired demyelinating sensory (DADS) neuropathy, can initially have a purely distal sensory presentation, although electrophysiological motor fiber involvement is common. Likewise, anti-myelin-associated glycoprotein (MAG) antibody neuropathy associated with IgM monoclonal gammopathy and the more recently described neuropathies with anti-paranodal autoantibodies[36] frequently present with distal and sensory-predominant concerns. In these cases, however, features consistent with demyelination are

typically detected on neurophysiology during the course of the disease, differentiating them from axonal DSP.

An exception to this is the more recently described and very severe neuropathy associated with antibodies to both forms of the neurofascin molecule, termed 'pan-neurofascin'.[37] These patients develop rapid tetraplegia, autonomic dysfunction, and respiratory involvement, and neurophysiology may show inexcitable nerves or features of severe axonal degeneration, due to the rapidity and severity of the condition.[37] Another recent study evaluating 55 patients with chronic neuropathies with anti-disialosyl ganglioside antibodies (CNDA) showed variability in the neurophysiological findings. Although a demyelinating polyradiculoneuropathy was seen in the majority (65%), a clinical and electrophysiological phenotype matching axonal sensory polyneuropathy was seen in 16%.[38]

These exceptions highlight that, although serological markers are absent in most forms of CIDP, and there are few reports of autoantibodies in sensory LFN, the recent discovery of paranodal autoantibodies and ongoing phenotyping of known antibody associated neuropathies highlights that antigenic targets remain undiscovered. Evaluation for autoantibodies in patients with LFN DSP is thus a potential avenue of future research.

Toxic and nutritional

Neurotoxic exposures are one of the earliest recognized causes of DSP.[39] The association between specific chemotherapy drugs and sensory neuropathy is so universally known that most patients with chemotherapy neuropathy are managed by oncologists rather than neurologists. Known neurotoxins include heavy metals, biotoxins, recreational toxins, industrial exposures, and medications (Table 1). Nutritional risks include deficiencies of thiamine or vitamin B12, long known to cause combined systems degeneration including DSP, myelopathy, optic nerve atrophy, cognitive impairment, and anemia. However, DSP

from nutritional deficiencies is becoming rare with greater caloric intake and mandated vitamin supplementation of specific foods. In contrast, toxicities from unsupervised vitamin "megadosing" are increasing in clinical practice as confirmed in a French cohort.[40] Vitamin B6 overdoses are a concern given links to sensory neuropathy (Table 1).[41]

Infectious and postinfectious including SARS-CoV-2 (COVID-19)

Direct infectious and indirect post-infectious causes of neuropathy have been known since antiquity, and mycobacterium leprae remains a major cause of DSP on the Indian subcontinent and in Brazil. Less common infections include cytomegalovirus, borrelia, and hepatitis C. Chagas (*Trypanosoma cruzi*) causes widespread or multifocal neuropathy with major autonomic involvement. In addition to acute neuronal infection, associated risks for DSP include potential neurotoxic releases by organisms, (e.g., diphtheria toxin), the body's inflammatory response to infection, potentially toxic effects of multiple anti-infective therapies, and critical care and malnutrition-associated neuropathy for the most gravely ill.

Potential associations between SARS-CoV-2 infection and DSP are of great current interest. Although sensory cell bodies, particularly the smaller-diameter ones, bear SARS-CoV-2 receptors,[42] autopsies do not reveal direct neuronal infection.[43] Currently, the leading potential culprits are a post-infectious inflammatory response in long-COVID symptoms,[44,45] with less-developed concerns about prolonged endothelial reactivity that might impair circulation into marginally perfused tissues such as the distal axon.[46] COVID-associated neuropathies can be subtyped into acute monophasic and chronic forms. More than 20% of acute COVID patients report transient neuropathy symptoms including paresthesias and pain in the extremities.

The largest current concern is potential associations between persistent "long-COVID" symptoms and DSP. Later, about 6% report neuropathy symptoms persisting

beyond 1-3 months after SARS-CoV-2 infection, although other persistent symptoms such as dysmotility, exertional intolerance, and cognitive dysfunction might include contributions from undiagnosed neuropathy.[47] Given considerable overlaps in symptoms, it is not unexpected that SFN is the most strongly associated in early case series. Among 17 patients with long COVID evaluated for neuropathy, skin biopsies identified SFN in 63%, along with one case each of critical care neuropathy and multifocal motor neuropathy.[48] However, there are no available data yet from large population surveys to confirm these preliminary observations.

Even less information is available about potential links with anti-COVID vaccines. However, analyses from the British National Immunoglobulin Database established a significant but small excess risk of acute demyelinating polyneuropathy (Guillain-Barre Syndrome) of 0.576 (95% CI 0.481-0.691) cases per 100,000 doses peaking at 24 days after administration of first-doses of ChAdOx1 nCoV-19 (AstraZeneca) vaccine only.[49] Given this, associations between specific COVID-19 vaccinations and DSP appear plausible, but are only supported by case reports so far.

Genetic

Very rare deterministic or Mendelian variants are long associated with sensory, motor, autonomic, demyelinating, and axonal neuropathy phenotypes. However, very few studies involving whole exome or whole genome screening (WES, WGS) have been conducted, so current knowledge is incomplete. Performing WGS in 23 unrelated Brazilian families with familial sensory neuropathy detected pathogenic variants in *ATL3*, *SPTLC2*, and *SCN9A* in 12 patients from five unrelated families.[50] There is also increasing understanding that more-common non-deterministic variants–for instance potentially affecting energy metabolism and immune responses–almost certainly contribute, but it can require genotyping thousands of

well phenotyped cases and healthy controls to identify them. New phenotypes are regularly described in case reports, but remain unconfirmed by population prevalence evaluation. Other aspects not currently captured include additive effects of more than one variant, interaction between variants and environmental risks, and neuropathy coexisting with other hereditary neurologic or multisystem disorders. Genetic testing is increasingly accessible and more widely available as next generation sequencing becomes less costly. Applying unbiased genetic sequencing to previously undifferentiated neuropathies is proving a rich vein of discovery, leading to new diagnostic categories described below.

When to order genetic testing

This decision remains challenging, and patient and clinician preferences are typically constrained by insurer restrictions. The increasing focus on development of genetic therapies pressures clinicians to avoid missing potentially treatable variants, but the implications of testing need to be carefully weighed. A genetic diagnosis can provide diagnostic certainty, abrogate further costly testing and ineffective medications, and allow participation in future clinical trials or natural history studies, not to mention guide family planning decisions. Additionally, hereditary transthyretin amyloidosis (hATTR) polyneuropathy has recently had specific targeted therapies approved for use. For the most part, however, there are still very few effective treatments for genetic neuropathies and confirming a genetic diagnosis might have adverse implications for insurance coverage or lead to discrimination. Perhaps the biggest current problem is ever-increasing patients with genetic variants of undetermined significance (VUS) in pathogenic or probably pathogenic genes. Ideally, specialists compare these with reported prevalences in genomics databases, the literature, the healthy population, and identify the location and predicted effects of each variant and evaluate a detailed family

history to assess potential pathogenicity, but such expertise is scarce, and time often not reimbursed.

Genetic testing methods continue to evolve, moving from targeted panels that report only on one or a few prespecified genes judged relevant to a neuropathy presentation, to unbiased whole exome (WES) or whole genome (WGS) sequencing. WES and WGS detect mutations missed by panels, however VUS detection increases, so too the potential to detect an unrelated medically significant diagnosis that may or may not be wanted. Raw sequences should be made available for future analyses by expert researchers with new discoveries, for periodic routine analysis, and for patients' potential future use for other purposes. Guidelines for evaluating variants are provided by the American College of Medical Genetics and Genomics, and many panels now include reflex secondary testing for their list of high-priority medical conditions.[51] It should be kept in mind that the rate of detecting pathological genetic mutations is currently only ~30% (in cases where CMT1A was pre-excluded), despite presenting with phenotypes suggesting an inherited neuropathy.[52] The highest priority for genetic testing is childhood-onset or clearly familial cases, or typical associating features. Genetic counseling is also recommended to help navigate this difficult terrain.

Hereditary Sensory Neuropathies

The hereditary sensory neuropathies (HSN, also called hereditary sensory and autonomic neuropathy (HSAN)), feature variable admixtures of sensory, autonomic and motor nerve involvement and historical names are not always accurate. Subdivision has occurred over time, with HSAN1 now divided into HSAN1A if the serine palmitoyltransferase long chain base subunit 1 (*SPTLC1*) gene mutation is found on 9q22.1-22.3[53] (OMIM #162400), HSAN1C for *SPTLC2* variants, and others. Interestingly, while mutations at multiple sites in the gene cause HSAN1, mutations in exon 2 cause familial amyotrophic lateral sclerosis by

an entirely different mechanism.[54] In HSAN2, a single exon within intron 8 of the lysine deficient protein kinase 1 (*WNK1*) gene on 12p13.33 (HSN2) is responsible for the condition now labeled HSAN2A (OMIM #201300). These conditions are included to highlight that the clinical phenotypes of hereditary neuropathies, regularly are further subdivided according to molecular diagnosis as genetic testing continues to increase, and the catalog of HSN mutations grows.

RFC1

The replication factor C subunit 1 (*RFC1*) on 4p14 (OMIM *102579) is a recently described gene with underappreciated implications for DSP. *RFC1* expansions were prevalent among 100 patients with cerebellar ataxia neuropathy and vestibular areflexia syndrome (CANVAS), in which one quarter had been labeled with sensory neuropathy alone.[55] A clue for clinicians is that chronic dry cough was reported in two thirds–and was the sole symptom in one third–up to 30 years pre-diagnosis.[55] Further exploration of an Australian cohort with neuropathy and/or ataxia found *RFC1* mutations in 5/17, most previously diagnosed with HSN and Sjögren's ganglionopathy.[56] Pathogenic RFC1 variants appear prevalent in initially idiopathic sensory neuropathy, including in 34% of patients with idiopathic chronic sensory axonal neuropathy,[57] of whom 42% had isolated sensory neuropathy with chronic cough.

Voltage-gated Sodium Channels (Na_v)

Variants in the 3 voltage-gated sodium channel expressed on nociceptive small fibers are implicated in the pathogenesis of dysfunctional nociceptive afferent neurons in painful DSP. Specifically, gain of function mutations in $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ alpha subunits encoded by *SCN9A* (OMIM *603415), *SCN10A* (OMIM *604427), and *SCN11A* (OMIM *604385) are associated with heterogenous clinical phenotypes that can include painful SFN,

small-fiber dysautonomia and other small-fiber symptoms and other concerns.[58] A recent Brazilian study using whole genome sequencing identified two new mutations.[50] Very rare patients have pathogenic variants in the auxiliary beta, rather than the alpha, sodium channel subunits, or loss-of-function variants associated with reduced pain sensitivity that can be lethal.[59,60] Two cases harboring new *SCN9A* variants with neuropathic pain and biopsy-proven SFN appeared to respond to intravenous immunoglobulin administered pre-testing,[61] though it is uncertain if this was coincidental. Small-fiber sodium channels have become a target of pharmaceutical investigation into new pain treatments. These examples highlight the complexity and rapid changes in this space, and readers are directed to a new online tool permitting evaluation of variants in all nine SCN-subtypes.[62]

Piezo-type Mechanosensitive Ion Channel Component 2 (PIEZO2)

PIEZO2 (OMIM *613629) is a recently described gene essential for mechanosensation, particularly light touch and proprioception.[63] Two patients loss-of-function variants in *PIEZO2* had severe progressive scoliosis, finger contractures, foot deformities and delayed motor milestones were found to have severe reduction in proprioception and vibratory sense, sensory ataxia and pseudoathetosis, but with preserved small-fiber pain/temperature, pressure, and itch sensations. The proposed mechanism in these patients, and later reported, is a profound deficit in mechanotransduction.[63]

Hereditary transthyretin amyloidosis (hATTR) polyneuropathy

Neuropathy is the commonest phenotype in this multisystem and heterogenous condition caused by extracellular deposition of amyloid fibrils due to mutation in the transthyretin gene.[64] Typical early symptoms include pain and paresthesia in the feet, along with autonomic symptoms, giving the appearance of a small fiber neuropathy,[65] and in the setting

of a strong family history may prompt consideration of HSAN. However, this condition invariably progresses to involve other organs and the large nerve fibers, and in more advanced stages of the disease will have a length-dependent sensorimotor axonal polyneuropathy clinically and neurophysiologically.[65] This condition is well-described, and is included here to also highlight the recent approval of genetic modifying therapies, which have revolutionized the management of this disabling condition[64] (see section on *Mechanism-targeting therapies* below).

Other associations

There is increasing evidence of secondary sensory nerve involvement in diverse conditions including primary motor disorders, movement disorders, and rheumatological conditions. A common question is to what extent these represent secondary "bystander" damage due to intense inflammation within nerves vs. neuronal mediation, perhaps though transsynaptic degeneration. For instance, ALS is a prototype motor neuropathy, however sensory nerve fiber pathology may be present as well. Skin biopsies from up to 80% of patients with sporadic ALS exhibit reductions in epidermal nerve fiber density (ENFD) versus age-matched controls.[66] It is unclear whether small fiber neuropathy in ALS arises from disease etiology or is a bystander from neurodegeneration more generally. Similarly, DSP is more prevalent in patients with PD compared with the normal population,[67] though mechanisms remain obscure. As levodopa disrupts homocysteine metabolism, it was initially suspected. However, reduced ENFD compared with healthy controls was found in a study of 85 PD patients, including 48 who were treatment naïve. Interestingly ENFD was lower on the more clinically affected side.[68]

Fibromyalgia

Fibromyalgia syndrome (FMS) is a non-specific label for a collection of symptoms. It does not fit the criteria for a disease, which requires a single underlying pathophysiology or pathology; thus it cannot be objectively diagnosed but only identified clinically.[69] Multiple different conditions have been associated with FMS, including SFN. Metanalysis reports abnormalities on skin biopsy are present in approximately 59% of studied patients, and corneal confocal microscopy (CCM) estimates abnormalities in around 45% of patients.[67,70] Similarly, 53% of patients with juvenile fibromyalgia had reduced ENFD (below 5%), in contrast to the predicted 4% of healthy controls.[71] The largest FMS study, of 117 women, reported 63% prevalence of low ENFD and other corroborating objective evidence including CCM.[72] Length and non-length-dependent SFN increasingly appears to be so prevalent in FMS that skin biopsy is worth considering in all fibromyalgia patients to better triage those with small-fiber neuropathy vs other underlying pathologies towards targeted further evaluation and treatments.

Advances in Diagnostic Testing

Because of the subjectivity and non-specificity of sensory and autonomic symptoms, patients typically benefit from objective confirmation of sensory findings, and these more strongly motivate clinicians to search for underlying causes and treat patients. Objective confirmation is also increasingly required for advanced or expensive therapies. However, testing may not be needed for clear-cut clinical presentations with typical symptoms and causes, very mild presentations, or patients not requiring treatment. Access and affordability of diagnostic testing is limited for almost all patients even in developed countries. This section prioritizes the emerging modalities of corneal confocal microscopy, magnetic resonance neurography, and ultrasound techniques, which are not routinely available. Nerve conduction studies

performed using portable equipment are the most widely available, and skin biopsies can be taken in any healthcare setting and mailed to specialty labs for processing and interpretation. It should be highlighted that these investigations are primarily useful for confirming the presence of neuropathy rather than a specific diagnosis that might lend itself to treatment, which usually requires the combination of clinical, examination, and other supportive investigation findings exploring causes as outlined above, including metabolic assessments, immune panels, and genetic panels.

Nerve conduction studies (NCS)

Electrodiagnostic nerve conduction studies, often performed with electromyography to assess motor axons and muscles, has long been the foundation of neuromuscular testing, and training and equipment are globally accessible to varying extents. NCS are the gold standard metric for motor and sensory large-fiber dysfunction.[73] DSP is characterized by reductions in amplitude with or without reduced conduction velocities of sensory nerve action potentials. In severe cases, the nerve will not respond to maximal stimulation. In pure SFN, NCS remain normal since they do not capture the small and slow electrical responses of stimulated small fibers.

Skin biopsy

The diagnostic workup for SFN, therefore, requires alternative methods, among which skin biopsy is most endorsed option.[3,74] Although expertise and special equipment are required, biopsies can be mailed to these labs from anywhere. A punch biopsy for measuring epidermal nerve fiber density (ENFD) is taken from the ankle approximately 10 cm above the lateral malleolus and in some cases on the distal thigh to increase sensitivity.[74] Bright field immunohistochemistry then permits visualizing ENFD. Measurements are then compared to

normative values, with values less than the 5th centile of predicted universally accepted as diagnostic for SFN. The major current limitation is that different labs use different comparator norms including diverse published binned values and lab-specific norms. Interpretative algorithms vary with different variables included or weighted differently. Sensitivity and specificity for skin biopsy in the diagnosis of SFN, when using clinical assessment as the gold standard, is approximately 80% and 90%.[74] However, the same biopsy can be interpreted differently by different labs, highlighting the need for consensus standards.

Quantitative sudomotor axon reflex test (QSART)

QSART increases the diagnostic yield in those with suspected SFN, whereas other tests including in the Mayo Clinic developed autonomic function testing panel are less strongly associated, except for tilt-table testing, which is less specific.[75] QSART measures postganglionic sympathetic sudomotor axon activity by infusing iontophoresed acetylcholine into the skin to stimulate cutaneous C-fibers and quantifying the resulting sweating response with a sensitivity of approximately 80%, assessed against current diagnostic criteria for SFN.[75] Assessing autonomic innervation is an important complement to skin biopsy testing of sensory axons. Expensive equipment and expertise limit use to specialty centers. Advanced patient preparation is required to optimize accuracy.

Quantitative sensory testing (QST)

QST assesses thermal and pain thresholds to determine functional impairment in both large and small nerve fibers.[76] Although it appears to be reproducible, there is a broad range of sensitivity and specificity estimates for QST in both large and small fiber neuropathy, calling into question the utility of its routine use in the clinical setting.[76] While some QST measures such as thermal thresholds correlate with ENFD, overall associations of QST measures with

DSP symptoms in remain weak.[77] QST might be best suited to monitor neuropathy longitudinally. A major limitation is that despite generating numbers, QST is not an objective test, but a refinement of sensory symptoms akin to pain scales. Furthermore, it is a time-consuming task requiring patient cooperation. Therefore in some settings including the U.S. it is not reimbursable as a clinical diagnostic test, limiting it to research use only.

Corneal Confocal Microscopy (CCM)

CCM non-invasively gathers objective pathology measurements of the density and branching complexity of nociceptive innervation of the cornea, by quantitating innervation in 'optical sections' of the cornea of living patients. The first CCM study of diabetic polyneuropathy found reduced corneal nerve fiber density (CNFD), corneal nerve fiber length (CNFL), and corneal nerve branch density (CNBD) versus matched healthy controls.[78] Several studies have replicated these findings, identifying additional metrics that correlate with ENFD pathology that gradually worsen in concert with neuropathy severity in diabetics with SFN symptoms.[79,80] CNBD, which is lower in diabetic patients without neuropathy, may be used to predict their development of neuropathy.[81] SFN findings may also correlate with CCM findings; 53% among 86 patients with clinical features suggestive of SFN had abnormal CCM results, which improved the diagnostic yield of skin biopsy alone from 70% to 85%.[82] This confirms an earlier study which found significant reductions in CNFD, CNFL, and CNBD in patients with idiopathic SFN when compared with healthy controls, even in the setting of normal QST findings.[83] Applying artificial intelligence and machine learning to CCM images of diabetic individuals achieved high precision in separating healthy controls from those with diabetes.[84] CCM requires ophthalmological expertise and complicated equipment, so availability is limited to a few centers expert in corneal research. As CCM

remains little studied in non-diabetic neuropathies and scalability and relative value have not been established, use is considered experimental at present.[3]

Ultrasound (US)

Neurologists are increasingly acquiring the portable equipment and training to perform nerve US in clinic. Standard parameters of cross-sectional area (CSA) and echogenicity of peripheral nerves appear to have similar diagnostic utility to comparable MR measurements, although both are currently experimental with more known about focal proximal nerve injuries than DSP which initiates at the thinnest, most dispersed axon terminals. Studying painful DSP associated with Sjogren's syndrome demonstrated comparable increased sural nerve CSA,[85] to skin biopsy testing, tentatively attributed to inflammatory infiltration.[86] In contrast, CANVAS patients had smaller median and ulnar nerve CSA than healthy controls, attributed to indicate axonal loss.[87] US measured nerve elasticity increases in some neural injuries[88] (Figure 3). It has also been shown to change along a gradient from healthy individuals (relatively high elasticity) to diabetic individuals without neuropathy (intermediate elasticity) and with neuropathy (relatively low elasticity) suggesting potential use in screening pre-symptomatic high-risk diabetic individuals.[89]

Magnetic Resonance Imaging (MRI)

MRI has the advantage of being non-invasive, and equipment and expertise are increasingly available. MR neurography (MRN), which uses high-resolution MRI in planes optimized to trace nerve plexi and major nerves is widely used to localize larger focal injuries. DSP is a newer indication under study. Parameters include changes in nerve caliber and signal suggestive of nerve fiber injury. However, accuracy/specificity is low so far.[90] Additional

methods being explored for DSP include diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI).

DTI (Figure 3) evaluates the apparent diffusivity of water molecules, which is unequally distributed in longitudinally oriented nerve. Diffusion is quantified with the use of fractional anisotropy (FA),[91] and DTI-derived measures including axial diffusivity (AD, along the axons) and radial diffusivity (RD, across the axons) may provide more specific information about axonal and myelin pathology.[92] In DSP, sensory axons contribute a smaller proportion to the volume-weighted mix of signals within a voxel in conventional imaging, making it more difficult to detect subtle changes in sensory nerves. Therefore, the improved specificity provided by DTI may improve our ability to detect these subtle changes.

MTI, often reported as a magnetization transfer ratio (MTR), is sensitive to changes in myelin density (Figure 3). It has been shown to correlate to disease severity in hereditary neuropathies.[93] MTR has also been studied in hereditary transthyretin amyloidosis polyneuropathy and compared with asymptomatic gene carriers as well as healthy controls.[94] MTR values were lowest in those with polyneuropathy and highest in healthy controls, and they correlated with clinical and neurophysiological markers.[94] Thus, MTR appears promising, clinically relevant, and may prove clinically useful in future studies of polyneuropathies.

Management Advances

Treating DSP should focus on reducing the patient's primary concern, improving their function, and remediating underlying damage where possible. Most DSP is multifactorial, so treating even one among several potential contributors can benefit patients. Lifestyle and medical improvements to general health and that improve nerve perfusion, such as smoking cessation, regular exercise, reducing cardiovascular limitations, and improved nutrition are

common targets. Symptomatic relief is often elusive as most treatments have only a 'medium' effect size. Earlier studies report tricyclics as having large effect sizes but modern studies are lacking because they are generic.[95] However, apparent high efficacy along with low cost, widespread availability, benefits for mood and sleep, and a half century of experience ensure continued use. Nortriptyline is supplanting amitriptyline given apparently equivalent efficacy and fewer adverse effects.[96] Given the high prevalence of DSP, it is attracting more interest from pharmaceutical companies, particularly for developing new patentable targeted therapies for select groups.

Management of neuropathic pain

Currently available agents

In 2021 American Academy of Neurology Guideline Subcommittee report updated the practice guideline for painful diabetic neuropathy,[95] which is by far best studied and the source of most information here. The 2020 consensus definition is intended to facilitate, standardize, and improve quality of clinical trials beyond diabetic neuropathy.[3]The neuropathic pain special interest group of the International Association for the Study of Pain also provides recommendations for managing neuropathic pain, which recommends tricyclics, calcium channel α2δ subunit ligands (gabapentinoids), and serotonin and norepinephrine reuptake inhibitors (SNRIs) as first line medications.[97] The guidelines suggest that as no one class among the recommended therapies performs significantly better; clinicians should select therapies guided by safety parameters, patient comorbidities, and concomitant medications. Affordability remains an important consideration. Medications with more than one therapeutic benefit are desired, for example in patients with pain, low mood, and/or sleep disturbance. Medications from different rather than the same class should

be tried if an initial medication is ineffective or poorly tolerated. Table 2 summarizes currently utilized therapies.

Complementary and alternative therapies

This vague concept typically refers to products and practices that are not part of standard, typically Western, medical care. It encompasses non-pharmacological interventions and interventions such as herbal preparations or supplements that may have pharmacological effects but are not regulated by federal agencies, so potency and potentially toxic contaminates vary. Non-pharmacological interventions for chronic pain include cognitive behavioral therapy, mindfulness-based approaches such as acceptance and commitment therapy, exercise, yoga, meditation, and acupuncture.[98,99] These interventions demonstrate a significant but typically only small improvement on rating scales assessing pain, quality of life measures, and severity of depression.[98,99] The antioxidants alpha-lipoic acid (ALA) and acetyl-L-carnitine reduce oxidative stress and may lessen pain in diabetic neuropathy, as measured by modest reductions in pain and disability scales.[98,100] Palmitoyl-ethanolamide (PEA) disrupts pain pathways including the expression of cyclooxygenase-2 (COX-2), and significantly reduces the neuropathy symptoms score, particularly when used in combination with ALA, by more than 3 points.[101] PEA may prevent demyelination via peroxisome proliferator-activated receptor alpha (PPAR-α);[102] however, there are no randomized controlled trials.

Cannabis and derivatives

Cannabis and its derivatives have been used medicinally throughout history and many DSP patients ask about them. Preparations, which vary globally, include tetrahydrocannabinol (THC) and cannabidiol (CBD) extracts for oromucosal administration, oils containing THC

or CBD alone, and synthetic cannabinoids such as nabilone that mimics THC. Whole cannabis is increasingly legal in various inhaled or oral products. However, studies evaluating cannabinoids for neuropathic pain began 15 years ago;[103] so many do not meet today's quality standards. A Cochrane review concluded that the potential benefits for chronic neuropathic pain might be outweighed by potential harms.[103] A 2021 systematic review found the best evidence was for single-day vaporized cannabis treatment in neuropathic pain, however cannabinoids were not consistently better than placebo in longer-term trials of neuropathic pain.[104] Studies of long-term use in DSP are lacking, as is evaluation for non-pain benefits such as for sleep, anxiety, and emotional well-being. Cannabinoid research appears high priority given global trends towards legalization and greater use.[105]

Neuromodulation: stimulation of spinal cord, DRG and brain

Spinal cord stimulation requires percutaneous insertion or occasional surgical implantation of a device to electrically stimulate the dorsal columns or dorsal root ganglia (DRG). It is thus a secondary treatment for pain refractory to medical approaches. Although mechanisms are uncertain, modulation of ascending pain signals or perhaps enhanced blood flow to the periphery are surmised.[106] High-frequency spinal cord stimulation (10kHz) improves pain and quality of life scores compared with best medical therapy.[107] Evidence in support of this procedure in DSP comes from two open-label RCTs relying on subjective markers of improvement, though in that context there was a reduction in pain by 50%.[107] Future studies with long-term follow up are needed. Interestingly, a randomized trial showed improved neurological examination findings, most markedly in sensory assessments, in 62% of patients, although there was no sham control group.[108] Safety concerns are typically limited to discomfort at the surgical site (8%), lead revision or replacement (6%) and wound infection (2%). Important considerations prior to recommending this procedure include MRI

incompatibility and possible decreased efficacy over time, the latter thought to occur due to scar formation or migration of stimulating leads. Only a few uncontrolled retrospective reports examine DRG stimulation in DSP. Although they report improved pain scores, this remains experimental at present.[109]

Brain stimulation is a rarely considered non-invasive option for intractable neuropathic pain, particularly non-invasive transcranial options. Repetitive transcranial magnetic stimulation (rTMS) is a viable option for treatment-resistant chronic neuropathic pain.[110] A randomized placebo-controlled cross-over trial in diabetic neuropathy reported efficacy against pain with benefits lasting up to 3 weeks post-stimulation.[111] rTMS may reduce neuropathic pain by inducing motor cortex plasticity and activating descending inhibitory pain control systems. Availability is limited as for all neuromodulatory treatments.

Mechanism-targeting therapies

SPTLC1

Pathogenic SPTLC1 gene mutations in HSAN1A alters preference of serine palmitoyltransferase activity towards synthesizing toxic sphingolipids.[112] L-serine, an inexpensive, widely available nutritional supplement, competitively restores equilibrium towards the normal substrate. A small placebo-controlled randomized trial of L-serine 400 mg/kg/day, reported a reduction in the CMT neuropathy scale by 1.5 points in contrast with the placebo group ($p=0.03$).[112] Despite this, the primary outcome of progression of neuropathy over one year was not statistically different between the groups. Factors included the small sample size and insufficient length, but above all the advanced neuropathy in primarily middle-aged patients with genetic abnormalities. The absence of adverse effects suggested the potential for a trial in HSAN1 children and young adults.

Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy

Extracellular aggregations of amyloid fibrils develop in multiple tissues in both hereditary and acquired amyloidosis, including peripheral nerves. hATTR includes rapidly progressive and disabling sensorimotor axonal neuropathy with early small-fiber involvement. The mainstay of therapy has been liver transplantation to reduce production of variant TTR, stabilization of the tetramer with TTR stabilizers including diflunisal and tafamidis, and TTR fibril removal through the combination of doxycycline and tauoursodeoxycholic acid (TUDCA). Genetic therapies, however, have revolutionized care. Antisense oligonucleotides (e.g. the subcutaneous preparation, inotersen) and small interfering RNAs (e.g. the intravenous preparation, patisiran; the subcutaneous preparation, vutisiran) decrease production of TTR by targeting RNA, such that mRNA and ultimately translation are reduced, leading to a decreased ability to generate new amyloid. They have been shown to improve markers of DSP, as well as quality of life and functional outcomes. The reader is directed to a recent review detailing established therapies and these recent genetic advances.[113]

Intravenous immunoglobulin for dysimmune neuropathies

Intravenous immunoglobulin (IVIg) is a primary treatment for multiple peripheral- and central nervous system conditions attributed to disordered immunity, including GBS, CIDP, and MMN. It has multiple immunoregulatory effects; on autoantibodies, complement activation, FcRn saturation, FcgammaRIIb receptors, cytokines, and inflammatory mediators.[114] The use of IVIg in conditions that are immune-based and coexist with DSP significantly improves symptoms. For instance, SFN associated with sarcoidosis responded to IVIg in 76% of patients, and Sjogren's- and celiac-associated small fiber neuropathy improved in case series, with return of symptoms on IVIg cessation in those with celiac

disease.[115] Two IVIg trials in patients with TS-HDS and FGFR-3 antibodies reported that 10/12 patients treated had improved pain scores and/or more ENFD on skin biopsy;[115] although, as outlined above, a more recent randomized controlled trial found no difference between IVIg and placebo in this same group.[32] An IVIg trial in SFN attributed to inflammatory/dysimmune causes, either because of a previously diagnosed autoimmune disorder, or the presence of one or more abnormal blood markers associated with autoimmunity, also showed efficacy: IVIg reduced QSART abnormalities from 70% to 50% and reduced 0-10 pain scores by one point.[116] A complimentary randomized placebo controlled trial of patients with idiopathic SFN that excluded patients with histories or markers of dysimmunity found no benefit for pain from IVIg.[117] Taken together, these studies seem to suggest that IVIg is effective in DSP when dysimmunity is present, and ineffective if those patients are excluded; although, more head-to-head trials are needed to definitively address this contention, particularly given the recent negative RCT. Given the high cost of IVIg, logistic difficulties, and rare adverse thrombotic events,[118] a high priority is to determine which patient populations should be eligible. Early-onset small fiber neuropathy in children and young adults requires difficult decisions given that up to 90% of cases appear to have dysimmune/inflammatory contributors[119], and potential life-long consequences of non-treatment. In a large series of young patients with definite or probable small fiber neuropathy, 80% of those with a history of autoimmunity of positive inflammatory blood test markers, without another cause of SFN, responded to corticosteroids or IVIg.[120]

Future directions

DSP remains difficult to manage, but the advances in the diagnostic approaches outlined in this review may improve case ascertainment and help associate more initially idiopathic DSP with potentially treatable conditions. Precision medicine is on the horizon, in which

individualized treatment approaches dependent on individual mechanisms may permit abrogate, delay, or prevent neuronal damage. More work is needed, however, on refining the metrics relevant to DSP, to more accurately and objectively characterize patients, identify causes, and track natural history and test new treatments more often and dependably.

Figures

Figure 1

(A) Normal skin biopsy demonstrating preservation of nerve fiber density, in this case 675 ENF/mm^2 skin surface area, in contrast to (B) which shows reduction in intraepidermal nerve fiber density to 155 ENF/mm^2, consistent with small fiber neuropathy. Scale bar represents 50μm. Images A and B were reproduced with permission from Journal Pediatrics, Vol. 131(4), Page e1091-e1100, Copyright © 2013 by the AAP. (C) Light microscopy of nerve biopsy demonstrates normal nerve architecture, in contrast to (D) which shows axonal loss consistent with axonal neuropathy, in this case amyloid associated neuropathy. (E) Typical clinical characteristics in DSP, as per Box 1.

Figure 2

Proposed cellular mechanisms leading to axonal injury and pain in neuropathy related to the metabolic syndrome.

Figure 3

Advanced imaging modalities for investigating DSP. Diffusion tensor imaging (A) in DSP shows a decreased FA, while mean diffusivity (MD) and radial diffusivity (RD) are increased in comparison to healthy controls. (B) Proton-density MRI scan of the thigh of a healthy subject (top) and patient with inherited neuropathy (bottom) with overlaid MTR maps of the sciatic nerve (zoomed inset). Note the reduction of MTR in the neuropathy patient, which is

likely reflective of changes in myelin content. Ultrasound elastography assessment of tibial nerve in a healthy control (C) and a patient with DSP (D) shows increased nerve stiffness in the neuropathy patient.

REFERENCES

1. Hanewinckel R, Drenthen J, van Oijen M, Hofman A, van Doorn PA, Ikram MA. Prevalence of polyneuropathy in the general middle-aged and elderly population. (1526-632X (Electronic)).
2. Hicks CW, Wang D, Windham BG, Matsushita K, Selvin E. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. *Scientific Reports.* 2021;11.
3. Freeman R, Gewandter JS, Faber CG, et al. Idiopathic distal sensory polyneuropathy: ACTTION diagnostic criteria. *Neurology.* 2020;95(22):1005-1014.
4. Camdessanché J-P, Jousserand G, Ferraud K, et al. The pattern and diagnostic criteria of sensory neuronopathy: a case–control study. *Brain.* 2009;132(7):1723-1733.
5. Gwathmey KG. Sensory neuronopathies. *Muscle Nerve.* 2016;53(1):8-19.
6. Callaghan BC, Price RS, Feldman EL. Distal Symmetric Polyneuropathy: A Review. *JAMA.* 2015;314(20):2172-2181.

7. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. (2056-676X (Electronic)).
8. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev.* 2012(6):CD007543.
9. Callaghan BC, Xia R, Reynolds E, et al. Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. *JAMA neurology.* 2016;73(12):1468-1476.
10. Callaghan BC, Feldman E, Liu J, et al. Triglycerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. *Diabetes Care.* 2011;34(3):635-640.
11. Look ARG. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. *Diabetologia.* 2017;60(6):980-988.
12. Rumora AE, Lentz SI, Hinder LM, et al. Dyslipidemia impairs mitochondrial trafficking and function in sensory neurons. *Faseb j.* 2018;32(1):195-207.
13. Rumora AE, LoGrasso G, Haidar JA, Dolkowski JJ, Lentz SI, Feldman EL. Chain length of saturated fatty acids regulates mitochondrial trafficking and function in sensory neurons. *J Lipid Res.* 2019;60(1):58-70.
14. Sajic M, Rumora AE, Kanhai AA, et al. High Dietary Fat Consumption Impairs Axonal Mitochondrial Function In Vivo. *J Neurosci.* 2021;41(19):4321-4334.
15. Feldman EL, Nave KA, Jensen TS, Bennett DLH. New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain. *Neuron.* 2017;93(6):1296-1313.
16. Andersen ST, Witte DR, Dalsgaard EM, et al. Risk Factors for Incident Diabetic Polyneuropathy in a Cohort With Screen-Detected Type 2 Diabetes Followed for 13 Years: ADDITION-Denmark. *Diabetes Care.* 2018;41(5):1068-1075.
17. Düll MM, Riegel K, Tappenbeck J, et al. Methylglyoxal causes pain and hyperalgesia in human through C-fiber activation. *Pain.* 2019;160(11):2497-2507.
18. Eid SA, El Massry M, Hichor M, et al. Targeting the NADPH Oxidase-4 and Liver X Receptor Pathway Preserves Schwann Cell Integrity in Diabetic Mice. *Diabetes.* 2020;69(3):448-464.
19. Veluchamy A, Hébert HL, van Zuydam NR, et al. Association of Genetic Variant at Chromosome 12q23.1 With Neuropathic Pain Susceptibility. *JAMA Netw Open.* 2021;4(12):e2136560.
20. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154.
21. O'Brien PD, Guo K, Eid SA, et al. Integrated lipidomic and transcriptomic analyses identify altered nerve triglycerides in mouse models of prediabetes and type 2 diabetes. *Dis Model Mech.* 2020;13(2):dmm042101.
22. Rumora AE, LoGrasso G, Hayes JM, et al. The Divergent Roles of Dietary Saturated and Monounsaturated Fatty Acids on Nerve Function in Murine Models of Obesity. *J Neurosci.* 2019;39(19):3770-3781.
23. Kristensen FP, Christensen DH, Callaghan BC, et al. Statin Therapy and Risk of Polyneuropathy in Type 2 Diabetes: A Danish Cohort Study. *Diabetes Care.* 2020;43(12):2945-2952.

24. Liampas A, Parperis K, Erotocritou MF, et al. Primary Sjögren syndrome-related peripheral neuropathy: A systematic review and meta-analysis. *Eur J Neurol.* 2022.
25. Dabby R, Weimer LH, Hays AP, Olarte M, Latov N. Antisulfatide antibodies in neuropathy: clinical and electrophysiologic correlates. *Neurology.* 2000;54(7):1448-1452.
26. Giannotta C, Di Pietro D, Gallia F, Nobile-Orazio E. Anti-sulfatide IgM antibodies in peripheral neuropathy: to test or not to test? *European Journal of Neurology.* 2015;22(5):879-882.
27. Yuki N, Chan AC, Wong AHY, et al. Acute painful autoimmune neuropathy: A variant of Guillain-Barre syndrome. *Muscle Nerve.* 2018;57(2):320-324.
28. Oaklander AL. Dysimmune Small Fiber Neuropathies. In: Rajabally YA, ed. *Dysimmune Neuropathies.* UK: Academic Press; 2020:225-247.
29. Levine TD, Kafaie J, Zeidman LA, et al. Cryptogenic small-fiber neuropathies: Serum autoantibody binding to trisulfated heparan disaccharide and fibroblast growth factor receptor-3. *Muscle Nerve.* 2020;61(4):512-515.
30. Fujii T, Lee EJ, Miyachi Y, et al. Antiplexin D1 Antibodies Relate to Small Fiber Neuropathy and Induce Neuropathic Pain in Animals. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(5):e1028.
31. Tholance Y, Moritz CP, Rosier C, et al. Clinical characterisation of sensory neuropathy with anti-FGFR3 autoantibodies. *J Neurol Neurosurg Psychiatry.* 2020;91(1):49-57.
32. Gibbons CH, Rajan S, Senechal K, Hendry E, McCallister B, Levine TD. A double-blind placebo-controlled pilot study of immunoglobulin for small fiber neuropathy associated with TS-HDS and FGFR-3 autoantibodies. *Muscle Nerve.* 2022.
33. Chan ACY, Wong HY, Chong YF, et al. Novel Autoantibodies in Idiopathic Small Fiber Neuropathy. *Annals of Neurology.* 2022;91(1):66-77.
34. Samara V, Sampson J, Muppidi S. FGFR3 Antibodies in Neuropathy: What to Do With Them? *J Clin Neuromuscul Dis.* 2018;20(1):35-40.
35. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. *Eur J Neurol.* 2021;28(11):3556-3583.
36. Garg N, Park SB, Vucic S, et al. Differentiating lower motor neuron syndromes. *Journal of Neurology, Neurosurgery, and Psychiatry.* 2017;88(6):474-483.
37. Querol L. Autoimmune nodopathies: treatable neuropathies beyond traditional classifications. *Journal of Neurology, Neurosurgery & Psychiatry.* 2021;92(10):1025-1025.
38. Peillet C, Adams D, Attarian S, et al. Anti-disialosyl-immunoglobulin M chronic autoimmune neuropathies: a nationwide multicenter retrospective study. *Eur J Neurol.* 2022;29(12):3547-3555.
39. Spencer PS, Schaumburg HH. *Experimental and Clinical Neurotoxicology.* 2nd ed. New York: Oxford University Press; 2000.
40. Dubuisson C, Dufour A, Carrillo S, Drouillet-Pinard P, Havard S, Volatier J-L. The Third French Individual and National Food Consumption (INCA3) Survey 2014–2015: method, design and participation rate in the framework of a European harmonization process. *Public health nutrition.* 2019;22(4):584-600.

41. Bossard V, Bourmeyster N, Pasini S, et al. Problematic rise of vitamin B6 supplementation overuse and potential risk to bariatric surgery patients. *Nutrition.* 2022;102:111738.
42. Shiers S, Ray PR, Wangzhou A, et al. ACE2 and SCARF expression in human dorsal root ganglion nociceptors: implications for SARS-CoV-2 virus neurological effects. *Pain.* 2020;161(11):2494-2501.
43. Suh J, Mukerji SS, Collens SI, et al. Skeletal muscle and peripheral nerve histopathology in COVID-19. *Neurology.* 2021;97(8):e849-e858.
44. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol.* 2022;23(2):194-202.
45. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol.* 2022.
46. Charfeddine S, Ibn Hadj Amor H, Jdidi J, et al. Long COVID 19 Syndrome: Is It Related to Microcirculation and Endothelial Dysfunction? Insights From TUN-EndCOV Study. *Front Cardiovasc Med.* 2021;8:745758.
47. Odozor CU, Kannampallil T, Ben Abdallah A, et al. Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study. *Pain.* 2022.
48. Oaklander AL, Mills AJ, Kelley M, et al. Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID. *Neurol Neuroimmunol Neuroinflamm.* 2022;9(3).
49. Keh RYS, Scanlon S, Datta-Nemdharry P, et al. COVID-19 vaccination and Guillain-Barre syndrome: analyses using the National Immunoglobulin Database. *Brain.* 2022.
50. Cintra VP, Dohrn MF, Tomaselli PJ, et al. Rare mutations in ATL3, SPTLC2 and SCN9A explaining hereditary sensory neuropathy and congenital insensitivity to pain in a Brazilian cohort. *J Neurol Sci.* 2021;427:117498.
51. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424.
52. Cortese A, Wilcox JE, Polke JM, et al. Targeted next-generation sequencing panels in the diagnosis of Charcot-Marie-Tooth disease. *Neurology.* 2020;94(1):e51-e61.
53. Houlden H, Blake J, Reilly MM. Hereditary sensory neuropathies. *Current Opinion in Neurology.* 2004;17(5):569-577.
54. Mohassel P, Donkervoort S, Lone MA, et al. Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis. *Nat Med.* 2021;27(7):1197-1204.
55. Cortese A, Tozza S, Yau WY, et al. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. *Brain: A Journal of Neurology.* 2020;143(2):480-490.
56. Kumar KR, Cortese A, Tomlinson SE, et al. RFC1 expansions can mimic hereditary sensory neuropathy with cough and Sjögren syndrome. *Brain.* 2020;143(10):e82.
57. Curro R, Salvalaggio A, Tozza S, et al. RFC1 expansions are a common cause of idiopathic sensory neuropathy. *Brain.* 2021;144(5):1542-1550.
58. Sopacua M, Hoeijmakers JGJ, Merkies ISJ, Lauria G, Waxman SG, Faber CG. Small-fiber neuropathy: Expanding the clinical pain universe. *J Peripher Nerv Syst.* 2019;24(1):19-33.

59. Alsaloum M, Labau JIR, Sosniak D, et al. A novel gain-of-function sodium channel beta2 subunit mutation in idiopathic small fiber neuropathy. *J Neurophysiol.* 2021;126(3):827-839.
60. Lischka A, Lassuthova P, Cakar A, et al. Genetic pain loss disorders. *Nat Rev Dis Primers.* 2022;8(1):41.
61. Kelley MA, Oaklander AL. Association of small-fiber polyneuropathy with three previously unassociated rare missense SCN9A variants. *Can J Pain.* 2020;4(1):19-29.
62. Brunklaus A, Feng T, Brunger T, et al. Gene variant effects across sodium channelopathies predict function and guide precision therapy. *Brain.* 2022:awac006.
63. Chesler AT, Szczot M, Bharucha-Goebel D, et al. The Role of PIEZO2 in Human Mechanosensation. *N Engl J Med.* 2016;375(14):1355-1364.
64. Carroll A, Dyck PJ, Carvalho Md, et al. Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. *Journal of Neurology, Neurosurgery & Psychiatry.* 2022.
65. Pinto MV, Dyck PJB, Liewluck T. Neuromuscular amyloidosis: Unmasking the master of disguise. *Muscle & Nerve.* 2021;64(1):23-36.
66. Truini A, Biasiotta A, Onesti E, et al. Small-fibre neuropathy related to bulbar and spinal-onset in patients with ALS. *Journal of Neurology.* 2015;262(4):1014-1018.
67. Ghasemi M, Rajabally YA. Small fiber neuropathy in unexpected clinical settings: a review. *Muscle & Nerve.* 2020;62(2):167-175.
68. Nolano M, Provitera V, Manganelli F, et al. Loss of cutaneous large and small fibers in naive and l-dopa-treated PD patients. *Neurology.* 2017;89(8):776-784.
69. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res(Hoboken).* 2010;62(5):600-610.
70. Grayston R, Czanner G, Elhadd K, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. *Semin Arthritis Rheum.* 2019;48(5):933-940.
71. Boneparth A, Chen S, Horton DB, et al. Epidermal Neurite Density in Skin Biopsies From Patients With Juvenile Fibromyalgia. *J Rheumatol.* 2021;48(4):575-578.
72. Evdokimov D, Frank J, Klitsch A, et al. Reduction of skin innervation is associated with a severe fibromyalgia phenotype. *Ann Neurol.* 2019;86(4):504-516.
73. Jensen TS, Karlsson P, Gylfadottir SS, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. *Brain.* 2021;144(6):1632-1645.
74. Lauria G, Hsieh ST, Johansson O, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol.* 2010;17(7):903-912, e944-909.
75. Thaisetthawatkul P, Fernandes Filho JA, Herrmann DN. Contribution of QSART to the diagnosis of small fiber neuropathy. *Muscle Nerve.* 2013;48(6):883-888.
76. Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain.* 2013;154(9):1807-1819.
77. Karlsson P, Hincker AM, Jensen TS, Freeman R, Haroutounian S. Structural, functional, and symptom relations in painful distal symmetric polyneuropathies: a systematic review. *Pain.* 2019;160(2).

78. Malik RA, Kallinikos P, Abbott CA, et al. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. *Diabetologia.* 2003;46(5):683-688.
79. Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes.* 2007;56(8):2148-2154.
80. Ferrari G, Nalassamy N, Downs H, Dana R, Oaklander AL. Corneal innervation as a window to peripheral neuropathies. *ExpEye Res.* 2013;113C:148-150. doi: 10.1016/j.exer.2013.05.016.:148-150.
81. Perkins BA, Lovblom LE, Lewis EJH, et al. Corneal Confocal Microscopy Predicts the Development of Diabetic Neuropathy: A Longitudinal Diagnostic Multinational Consortium Study. *Diabetes Care.* 2021;44(9):2107-2114.
82. Egenolf N, Zu Altenschildesche CM, Kress L, et al. Diagnosing small fiber neuropathy in clinical practice: a deep phenotyping study. *Ther Adv Neurol Disord.* 2021;14:17562864211004318.
83. Tavakoli M, Marshall A, Pitceathly R, et al. Corneal confocal microscopy: a novel means to detect nerve fibre damage in idiopathic small fibre neuropathy. *Exp Neurol.* 2010;223(1):245-250.
84. Preston FG, Meng Y, Burgess J, et al. Artificial intelligence utilising corneal confocal microscopy for the diagnosis of peripheral neuropathy in diabetes mellitus and prediabetes. *Diabetologia.* 2022;65(3):457-466.
85. Yoshida T, Nodera H, Kumon Y, Osanai S, Izumi Y, Mizukami H. Detection of nerve enlargement with ultrasound and correlation with skin biopsy findings in painful sensory neuropathy associated with Sjogren's syndrome. *Mod Rheumatol.* 2021;31(4):849-855.
86. Ebadi H, Siddiqui H, Ebadi S, Ngo M, Breiner A, Bril V. Peripheral Nerve Ultrasound in Small Fiber Polyneuropathy. *Ultrasound Med Biol.* 2015;41(11):2820-2826.
87. Pelosi L, Leadbetter R, Mulroy E, Chancellor AM, Mossman S, Roxburgh R. Peripheral nerve ultrasound in cerebellar ataxia neuropathy vestibular areflexia syndrome (CANVAS). *Muscle & Nerve.* 2017;56(1):160-162.
88. Wee TC, Simon NG. Ultrasound elastography for the evaluation of peripheral nerves: A systematic review. *Muscle & Nerve.* 2019;60(5):501-512.
89. Ishibashi F, Taniguchi M, Kojima R, Kawasaki A, Kosaka A, Uetake H. Elasticity of the tibial nerve assessed by sonoelastography was reduced before the development of neuropathy and further deterioration associated with the severity of neuropathy in patients with type 2 diabetes. *J Diabetes Investig.* 2016;7(3):404-412.
90. Aggarwal A, Srivastava DN, Jana M, et al. Comparison of Different Sequences of Magnetic Resonance Imaging and Ultrasonography with Nerve Conduction Studies in Peripheral Neuropathies. *World Neurosurgery.* 2017;108:185-200.
91. Manzanera Esteve IV, Farinas AF, Pollins AC, et al. Noninvasive diffusion MRI to determine the severity of peripheral nerve injury. *Magn Reson Imaging.* 2021;83:96-106.
92. Manzanera Esteve IV, Farinas AF, Pollins AC, et al. Noninvasive diffusion MRI to determine the severity of peripheral nerve injury. *Magn Reson Imaging.* 2021;83:96-106.
93. Dortch RD, Dethrage LM, Gore JC, Smith SA, Li J. Proximal nerve magnetization transfer MRI relates to disability in Charcot-Marie-Tooth diseases. *Neurology.* 2014;83(17):1545-1553.

94. Kollmer J, Hegenbart U, Kimmich C, et al. Magnetization transfer ratio quantifies polyneuropathy in hereditary transthyretin amyloidosis. *Ann Clin Transl Neurol.* 2020;7(5):799-807.
95. Price R, Smith D, Franklin G, et al. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary: Report of the AAN Guideline Subcommittee. *Neurology.* 2022;98(1):31-43.
96. Watson CPN, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology.* 1998;51(4):1166-1171.
97. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173.
98. Baute V, Zelnik D, Curtis J, Sadeghifar F. Complementary and Alternative Medicine for Painful Peripheral Neuropathy. *Curr Treat Options Neurol.* 2019;21(9):44.
99. Davoudi M, Taheri AA, Foroughi AA, Ahmadi SM, Heshmati K. Effectiveness of acceptance and commitment therapy (ACT) on depression and sleep quality in painful diabetic neuropathy: a randomized clinical trial. *J Diabetes Metab Disord.* 2020;19(2):1081-1088.
100. Agathos E, Tentolouris A, Eleftheriadou I, et al. Effect of alpha-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. *J Int Med Res.* 2018;46(5):1779-1790.
101. Pieralice S, Vari R, Minutolo A, et al. Biomarkers of response to alpha-lipoic acid +/- palmitoiletanolamide treatment in patients with diabetes and symptoms of peripheral neuropathy. *Endocrine.* 2019;66(2):178-184.
102. Di Cesare Mannelli L, D'Agostino G, Pacini A, et al. Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR-alpha-mediated mechanism. *Mediators Inflamm.* 2013;2013:328797.
103. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.
104. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. *Pain.* 2021;162(Suppl 1):S45-s66.
105. Haroutounian S, Arendt-Nielsen L, Belton J, et al. International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. *Pain.* 2021;162(Suppl 1):S117-s124.
106. van Beek M, Hermes D, Honig WM, et al. Long-Term Spinal Cord Stimulation Alleviates Mechanical Hypersensitivity and Increases Peripheral Cutaneous Blood Perfusion in Experimental Painful Diabetic Polyneuropathy. *Neuromodulation.* 2018;21(5):472-479.
107. Duarte RV, Nevitt S, Maden M, et al. Spinal cord stimulation for the management of painful diabetic neuropathy: a systematic review and meta-analysis of individual patient and aggregate data. *Pain.* 2021;162(11).
108. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of High-frequency (10-kHz) Spinal Cord Stimulation in Patients With Painful Diabetic Neuropathy: A Randomized Clinical Trial. *JAMA neurology.* 2021;78(6):687-698.

109. D'Souza RS, Langford B, Dombovy-Johnson M, Abd-Elsayed A. Neuromodulation Interventions for the Treatment of Painful Diabetic Neuropathy: a Systematic Review. *Curr Pain Headache Rep.* 2022;26(5):365-377.
110. Attia M, McCarthy D, Abdelghani M. Repetitive Transcranial Magnetic Stimulation for Treating Chronic Neuropathic Pain: a Systematic Review. *Curr Pain Headache Rep.* 2021;25(7):48.
111. Onesti E, Gabriele M, Cambieri C, et al. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. *EurJPain.* 2013:10-2149.
112. Fridman V, Suriyanarayanan S, Novak P, et al. Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. *Neurology.* 2019;92(4):e359-e370.
113. Carroll A, Dyck PJ, de Carvalho M, et al. Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. *J Neurol Neurosurg Psychiatry.* 2022;93(6):668-678.
114. Dalakas MC. Update on intravenous immunoglobulin in neurology: Modulating neuro-autoimmunity, evolving factors on efficacy and dosing and challenges on stopping chronic IVIg therapy. *Neurotherapeutics.* 2021;18(4):2397-2418.
115. Zeidman LA. Advances in the Management of Small Fiber Neuropathy. *Neurologic Clinics.* 2021;39(1):113-131.
116. Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. *Therapeutic Advances in Neurological Disorders.* 2018;11:1756285617744484.
117. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy. *Neurology.* 2021;96(20):e2534.
118. Kapoor M, Hunt I, Spillane J, et al. IVIg-exposure and thromboembolic event risk: findings from the UK Biobank. *J Neurol Neurosurg Psychiatry.* 2022.
119. Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240-1251.
120. Oaklander AL, Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. *Pediatrics.* 2013;131(4):e1091-1100.

COMPETING INTERESTS STATEMENT

Dr Silsby reports no competing interests.

Dr Feldman reports no competing interests.

Dr Dortch reports no competing interests.

Dr Rowe reports no competing interests.

Dr Haroutounian reports personal fees from Rafa Laboratories, Vertex Pharmaceuticals, and GW Pharmaceuticals, and research grants from Eli Lilly, outside the scope of this work.

Dr Rajabally has received speaker/consultancy honoraria from LFB, Polyneuron and Argenx and has received educational sponsorships from LFB and CSL Behring and has obtained research grants from LFB and CSL Behring.

Dr Vucic reports no competing interests.

Dr Shy has no competing interests related to this publication. He serves as a consultant for Applied Therapeutics, DTx Pharma, Mitochondria in Motion, Swan Biosci and Inflectis.

Dr Oaklander reports no competing interests.

Dr Simon reports no competing interests.