Diagnosing and managing diabetic somatic and autonomic neuropathy

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Abstract: The diagnosis and management of diabetic neuropathy can be a major challenge. Late diagnosis contributes to significant morbidity in the form of painful diabetic neuropathy, foot ulceration, amputation, and increased mortality. Both hyperglycaemia and cardiovascular risk factors are implicated in the development of somatic and autonomic neuropathy and an improvement in these risk factors can reduce their rate of development and progression. There are currently no US Food and Drug Administration (FDA)-approved disease-modifying treatments for either somatic or autonomic neuropathy, as a consequence of multiple failed phase III clinical trials. While this may be partly attributed to premature translation, there are major shortcomings in trial design and outcome measures. There are a limited number of partially effective FDA-approved treatments for the symptomatic relief of painful diabetic neuropathy and autonomic neuropathy.

Keywords: diabetic neuropathy, autonomic neuropathy, diagnosis, treatment

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Introduction
Diabetic peripheral neuropathy (DPN) occurs as a consequence of damage to the sensory, autonomic and motor nerves and can present with diverse symptoms and deficits (Table 1). The commonest presentations are those of somatic and autonomic neuropathy, and early diagnosis of these subtypes is recommended.1 Small-fibre neuropathy can develop in patients with impaired glucose tolerance (IGT),2 particularly those who develop type 2 diabetes mellitus (T2DM),3 and it is recommended that patients with peripheral neuropathy should be evaluated for glucose dysmetabolism. However, the methods currently advocated to diagnose DPN, for example, neurological exam, monofila-
ment and vibration sensation, detect moderate-to-severe large-fibre neuropathy, missing early small-fibre neuropathy.4 Other causes of neuropathy, including B12 deficiency, and inflammatory neuropathies must be actively sought, as they are potentially treatable.5,6 It is generally held that motor problems arise late in diabetic neuropathy, however recent studies show reduced muscle strength, volume and altered gait in patients with IGT and T2DM.7–9 Furthermore, acute-onset severe pain and swelling in a proximal muscle, should also alert the physician to the occurrence of diabetic muscle infarction.10 There is a threefold to fivefold higher prevalence of cranial11 and peripheral mononeuropathies in patients with diabetes. Carpal tunnel syndrome is the commonest mononeuropathy in patients with diabetes12 due to increased microangiopathy and vascular endothelial growth factor expression.13,14 While bracing and splinting relieve pain, carpal tunnel decompression surgery outcomes are excellent and associated with recovery of neurophysiological function in patients with diabetes.15

Disease-modifying therapies for DPN
Improved glycaemic control can prevent the progression of diabetic neuropathy in T1DM, but not in T2DM.16 This surprising result may be attributed to...
late and less effective lowering of glucose in patients with T2DM and established neuropathy, concomitant weight gain and hypoglycaemia, and the use of insensitive endpoints.17,18 Most of the studies assessing the effect of improved glycaemic control on neuropathy in T2DM were neither powered nor designed to show a benefit on neuropathy.16 Cardiovascular risk factors, especially hypertension and triglycerides have been shown to play an important role in the development of diabetic neuropathy.19 The STENO-2 study showed the overwhelming benefit of multifactorial risk factor reduction on cardiovascular outcomes,20 mortality,21 retinopathy, nephropathy and autonomic neuropathy, but not somatic neuropathy, as vibration perception was the endpoint for assessing neuropathy.22 Indeed, a recent Japanese study has shown that intensive multifactorial intervention which led to an almost normalization of glycosylated haemoglobin (HbA1c) with weight loss and a reduction in blood pressure showed a significant improvement in neurophysiology and small-nerve-fibre repair, assessed using corneal confocal microscopy,23 echoing the results of a previous study.24 Early diagnosis and intervention may also be the key, as lifestyle intervention in patients with prediabetes improved sudomotor function and intraepidermal nerve-fibre density.25 Indeed, smaller studies which have utilized more rigorous endpoints have shown a significant benefit on neurophysiology after treatment with an angiotensin-converting enzyme (ACE) inhibitor26 and on neurological deficits and neurophysiology after treatment with an ACE inhibitor and calcium-channel blocker.27 Statins or fibrates can also prevent the development of DPN,28,29 reduce diabetic foot infection,30 lower-extremity amputation31,32 and increase healing of foot ulcers.33 A post hoc analysis of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) study has shown that the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide reduced ulcer-related foot amputation.34 There are compelling experimental data showing a direct benefit of GLP-1 agonists on neuropathy.35−37 This would suggest that the GLP-1 agonists may have potential benefits in the treatment of diabetic neuropathy38 and a randomized clinical trial with rigorous endpoints is required to show this. The lack of rigorous and sensitive endpoints,4 recruitment of patients with a broad spectrum of neuropathy severity and short trial durations have contributed to the failure of clinical trials in DPN.17 Accurate phenotyping to select and stratify patients using sensitive endpoints targeting small-fibre repair (corneal confocal microscopy, skin biopsy) may allow trials of shorter duration to show an initial therapeutic effect. This would provide pharmaceutical companies with a go–no–go signal to invest in larger and longer trials, to gain US Food and Drug Administration (FDA) approval of disease-modifying therapies for DPN.18

### Table 1. Presentations of diabetic neuropathy.

| **Diabetic sensorimotor polyneuropathy** |
|------------------------------------------|
| Predominantly small-fibre neuropathy     |
| Predominantly large-fibre neuropathy     |
| Mixed small and large-fibre neuropathy (commonest) |

| **Atypical neuropathy** |
|-------------------------|
| Isolated cranial neuropathy [III, IV, VI, VII] |
| Mononeuropathy [ulnar, median, peroneal] |
| **Radiculopathy** |
| Lumbosacral radiculoplexus neuropathy [amyotrophy] |
| Cervical/thoracic radiculopathy |
| **Motor neuropathy** |
| Reduced muscle volume and strength |
| Muscle infarction |

Painful diabetic neuropathy

Painful diabetic neuropathy (PDN), a manifestation of small-fibre damage38–40 is characterized by burning pain and significantly impacts on the patient’s quality of life,41−43 due to associated depression, anxiety and sleep disturbance.42 It can affect 14.0–65.3% of patients with diabetes,41,44–49 and the broad prevalence rates are attributed to different populations, risk factors and diagnostic methods. Paradoxically, the prevalence of painful symptoms may be higher in south Asians, despite a lower overall prevalence of neuropathy50 and small-fibre neuropathy.51 Despite the availability of a number of questionnaires, for example, the Douleur Neuropathique 4 (DN4) questionnaire,52 Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale53 and Neuropathic Pain Questionnaire (NPQ),54 a large proportion of patients with PDN remain undiagnosed,55,56 and ‘suffer in silence’.57 The risk factors for painful diabetic neuropathy include older age, duration of diabetes, presence of diabetic peripheral neuropathy,41,44–46 obesity,41,45,56,58 smoking,44,58 poor glycaemic control,59,60 low high-density lipoprotein (HDL) cholesterol,41 elevated low-density lipoprotein (LDL) cholesterol, triglycerides and creatinine,47 and vitamin D deficiency.61,62
Treatment of PDN

There is no evidence that improvement in glyce-
mic control improves PDN; indeed, the oppo-
site is true, where rapid and large reductions in
HbA1c may precipitate an acute painful neu-
ropathy.63 The treatment of PDN has relied on
trying different moderately effective therapies
until one works, with minimal side effects. How-
ever, improved genotyping64,65 and clinical
phenotyping66 may allow targeted mechanism-
based therapies. Identifying patients with an
irritable nociceptor can reduce the number
needed to treat (NNT) for oxcarbazepine to 3.9
compared with 6.9 in patients with the nonirri-
table nociceptor.67 Similarly, identifying patients
with altered rate-dependent depression (RDD),
a marker of descending inhibitory pathway dys-
function, may focus on those who will respond
optimally to selective norepinephrine-reuptake
inhibitors, for example, duloxetine.68

Tricyclic antidepressants (TCAs) mediate analge-
sic efficacy by indirectly modifying the opioid sys-
tem in the brain and via neuromodulation of
serotonin and noradrenaline.69−71 A systematic
review of 17 studies involving amitriptyline in 1342
participants in PDN trials showed moderate effi-
cacy and caution, as there was a high risk of bias
due to the small participant numbers in each
study.72 Duloxetine and venlafaxine potentiate the
descending inhibitory pathways,73 and a Cochrane
review of eight randomized controlled trials
(RCTs) with 2728 participants showed that dulox-
etine 60mg daily had an NNT of five.74 Although
gabapentin is not FDA approved for the treatment of
PDN, a recent Cochrane review has shown effi-
cacy of this medication in DPN and it is widely
prescribed. However, somnolence and dizziness
limit dose titration and most patients do not receive
the doses (1200−3600mg) that have been shown to
be efficacious.75 Pregabalin is FDA approved for
PDN, based on a number of RCTs.76−78 Mirogabalin
has recently shown efficacy and good tolerability in
a phase II and two phase III clinical trials in
DPN.79−81 Tramadol may also be used second
line, but a Cochrane review found that the efficacy
of tramadol was determined in small inadequately-
sized studies, with a risk of bias.82 Tapentadol
extended release is only the third medication to be
recommended by the FDA for PDN.83−86 The
COMBO-DN study showed comparable neuro-
pathic pain outcomes between a combination of
duloxetine 60mg daily and pregabalin 300mg
daily, compared with high-dose monotherapy of
either duloxetine 120mg daily or pregabalin
600mg daily.87 Furthermore, in an exploratory post
hoc analysis, high-dose monotherapy was more
favourable in patients with severe pain, whereas
combination therapy was more beneficial in
patients with mild-to-moderate pain.88 There are
few head-to-head studies comparing different
drugs, but in a double-blind RCT in patients with
PDN, analgesic efficacy was comparable between
amitriptyline, duloxetine and pregabalin.89 We
have recently shown that treatment with vitamin D
improves the severity of neuropathic pain90 and
quality of life in patients with PDN.91

Autonomic neuropathy

Autonomic neuropathy is characterized by a range of
symptoms and signs, which can be debilitating in a
minority of patients, especially females with T1DM
(Table 2). Cardiac autonomic neuropathy (CAN) per se is the strongest risk factor for all-cause mortal-
ity in T1DM and was an independent risk factor for
mortality in the ACCORD study of patients with
T2DM.92,93 Hence, screening for CAN is recom-
mended at diagnosis in T2DM and after 5 years in

### Table 2. Symptoms and deficits in diabetic autonomic neuropathy.

| Cardiac autonomic neuropathy                  |
|----------------------------------------------|
| Resting tachycardia and/or fixed HR          |
| Nondipping of nocturnal systolic BP          |
| Orthostatic hypotension                      |
| Exercise intolerance                         |
| Syncope and light headedness                 |
| Painless myocardial infarction               |
| Arrhythmias                                  |
| **Sudomotor neuropathy**                     |
| Anhidrosis                                   |
| Gustatory sweating                           |
| **Urogenital autonomic neuropathy**          |
| Bladder dysfunction                          |
| 1. Nocturnal frequency and urgency           |
| 2. Urinary hesitancy, weak stream, dribbling |
| and urinary incontinence                     |
| Sexual dysfunction                           |
| Male: erectile dysfunction, decreased libido  |
| and retrograde ejaculation                    |
| Female: decreased sexual desire and arousal, |
| inadequate lubrication                       |
| **Gastrointestinal autonomic neuropathy**    |
| Nausea/vomiting                              |
| Bloating with inability to eat a full meal   |
| Increased variability in blood sugar and hypos|
| Nocturnal diarrhoea                          |

BP, blood pressure; HR, heart rate.
T1DM.1 The diagnosis of CAN includes documentation of the symptoms and signs, although there is a weak correlation between symptoms and autonomic deficits.94,95 Cardiovascular autonomic reflex testing (CARTs) includes heart rate response to deep breathing, standing and the Valsalva manoeuvre.96

**Disease-modifying therapies for autonomic neuropathy**

The DCCT showed that intensive glycaemic control in patients with T1DM reduced the development of CAN by 45%97 and the STENO-2 trial showed that intensified multifactorial treatment in patients with type 2 diabetes reduced the risk of CAN progression by 68%.98,99 A small early study found favourable effects of alpha-lipoic acid (ALA) on CAN,100 but a more recent study of triple antioxidant therapy (allopurinol, ALA and nicotinamide) showed no benefit.101 There are currently no FDA-approved disease-modifying treatments for CAN.

**Orthostatic hypotension**

Symptoms of orthostatic hypotension (OH) occur on standing and include light headedness, weakness, giddiness and syncope. OH is defined as a blood pressure fall on standing >20/10 mmHg (>30/15 mmHg in those with BP >150/90 mmHg) without an increase in heart rate (<15 beats per minute).102 Treatment of OH involves fluid and salt repletion and encouragement of physical activity to avoid deconditioning.103,104 Fludrocortisone is used but is not FDA approved for OH, and there are concerns over supine hypertension, hypokalaemia, congestive cardiac failure and peripheral oedema.105 Both midodrine and droxidopa are approved by the FDA for the treatment of symptomatic neurogenic OH.106

**Gastroparesis**

Gastroparesis may present with bloating, nausea and overt recurrent vomiting, necessitating admission to hospital, or may underlie unexplained variability in blood sugars. It is defined as the delayed removal of stomach contents in the absence of a physical obstruction.107 Gastric emptying should be formally assessed at 15-min intervals, with scintigraphy 4h after food intake of digestible solids. Metoclopramide is the only FDA-approved drug for the treatment of gastroparesis, but limited efficacy and the risk of tardive dyskinesia has led the FDA and European Medicines agency to limit its use to a maximum of 5 days. New therapies currently being investigated include motilin-receptor agonists, ghrelin-receptor agonists, and neurokinin-receptor antagonists. Mechanical options for intervention include transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy and in severe intractable gastroparesis, laparoscopic pyloroplasty or gastrectomy may be options.108

**Diabetic diarrhoea**

Diarrhoea occurs twice as frequently in diabetic patients and of course may be related to pancreatic exocrine insufficiency, bariatric surgery, and drugs such as metformin and GLP-1 agonists.109,110 Pharmacological therapies include antibiotics to eradicate bacterial overgrowth, somatostatin analogues, and selective serotonin 5-hydroxy tryptamine type 3 (HT3) receptor antagonists.111,112

**Bladder dysfunction**

Bladder dysfunction may occur in 50% of patients with diabetes due to urogenital autonomic neuropathy.113 Increased initiating threshold for the micturition reflex is followed by decreased detrusor activity and incomplete bladder emptying. The diagnosis should be based on urodynamic studies and the assessment of residual bladder volume. Treatment includes suprapubic pressure, intermittent self-catheterization, anticholinergic medication for detrusor hyperreflexia and parasympathomimetic medication to reduce detrusor contractility.114

**Sudomotor dysfunction**

A reduction or loss of distal sweating due to sympathetic derervation of the sweat glands is common115,116 and can precipitate a break in the skin, leading to foot ulceration. It can be assessed using neuropad®117−119 (Miro Verbandstoffe, Wiehl, Germany) or Sudoscan™120 Impeto Medical, Paris, France to risk stratify patients with DPN.121

**Erectile dysfunction**

Erectile dysfunction (ED) in patients with diabetes is three times more prevalent, may occur 10–15 years earlier and is less responsive to treatment, compared to patients without diabetes.122 ED is associated with a higher HbA1c, presence of metabolic syndrome, hypertension, dyslipidaemia,
lower estimated glomerular filtration rate, higher albumin/creatinine ratio and more severe small-fibre neuropathy.\textsuperscript{123–125} Around 47\% of women with diabetic neuropathy also have sexual dysfunction characterized by reduced sexual arousal, decreased lubrication and painful intercourse.\textsuperscript{126} Recent recommendations include active smoking cessation (improves ED by ~30\%), testosterone replacement in those with testosterone deficiency, statins, phosphodiesterase type 5 inhibitors, intracavernosal and transurethral prostaglandins, and penile implants for more severe cases.\textsuperscript{127–129}

Diabetic somatic and autonomic neuropathy have a significant impact on morbidity and mortality in the diabetic patient and yet remain woefully underdiagnosed and inadequately managed. Although there are currently no FDA-approved disease-modifying therapies, there is evidence that improvement in vascular risk factors alongside glycaemia may have a beneficial effect. Moderate relief of symptomatic, painful and autonomic neuropathy is possible, but requires early recognition and tailored intervention.

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The authors declare that there is no conflict of interest.

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**References**

1. Pop-Busui R, Boulton AJ, Feldman EL, \textit{et al.} Diabetic neuropathy: a position statement by the American Diabetes Association. \textit{Diabetes Care} 2017; 40: 136–154.

2. Asghar O, Petropoulos IN, Alam U, \textit{et al.} Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance. \textit{Diabetes Care} 2014; 37: 2643–2646.

3. Azmi S, Ferdousi M, Petropoulos IN, \textit{et al.} Corneal confocal microscopy identifies small-fiber neuropathy in subjects with impaired glucose tolerance who develop type 2 diabetes. \textit{Diabetes Care} 2015; 38: 1502–1508.

4. Malik RA. Which test for diagnosing early human diabetic neuropathy? \textit{Diabetes} 2014; 63: 2206–2208.

5. Martinelli-Boneschi F, Colombi M, Castori M, \textit{et al.} COL6A5 variants in familial neuropathic chronic itch. \textit{Brain} 2017; 140: 555–567.

6. Rajabally YA, Stettner M, Kieseier BC, \textit{et al.} CIDP and other inflammatory neuropathies in diabetes - diagnosis and management. \textit{Nat Rev Neurol} 2017; 13: 599–611.

7. Alam U, Riley DR, Jugdey RS, \textit{et al.} Diabetic neuropathy and gait: a review. \textit{Diabetes Ther} 2017; 8: 1253–1264.

8. Almurdhi MM, Brown SJ, Bowling FL, \textit{et al.} Altered walking strategy and increased unsteadiness in participants with impaired glucose tolerance and type 2 diabetes relates to small-fibre neuropathy but not vitamin D deficiency. \textit{Diabet Med} 2017; 34: 839–845.

9. Almurdhi MM, Reeves ND, Bowling FL, \textit{et al.} Reduced lower-limb muscle strength and volume in patients with type 2 diabetes in relation to neuropathy, intramuscular fat, and vitamin D levels. \textit{Diabetes Care} 2016; 39: 441–447.

10. Yong TY and Khow KSF. Diabetic muscle infarction in end-stage renal disease: a scoping review on epidemiology, diagnosis and treatment. \textit{World J Nephrol} 2018; 7: 58–64.

11. Watanabe K, Hagura R, Akanuma Y, \textit{et al.} characteristics of cranial nerve palsies in diabetic patients. \textit{Diabetes Res Clin Pract} 1990; 10: 19–27.

12. Calandruccio JH and Thompson NB. Carpal tunnel syndrome: making evidence-based treatment decisions. \textit{Orthop Clin North Am} 2018; 49: 223–229.

13. Mojaddidi MA, Ahmed MS, Ali R, \textit{et al.} Molecular and pathological studies in the posterior interosseous nerve of diabetic and non-diabetic patients with carpal tunnel syndrome. \textit{Diabetologia} 2014; 57: 1711–1719.

14. Thomsen NO, Mojaddidi M, Malik RA, \textit{et al.} Reduced myelinated nerve fibre and
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endoneurial capillary densities in the forearm of diabetic and non-diabetic patients with carpal tunnel syndrome. *Acta Neuropathol* 2009; 118: 785–791.

15. Thomsen NOB, Andersson GS, Bjork J, et al. Neurophysiological recovery 5 years after carpal tunnel release in patients with diabetes. *Muscle Nerve* 2017; 56: E59–E64.

16. Callaghan BC, Little AA, Feldman EL, et al. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012; 6: CD007543.

17. Malik RA. Why are there no good treatments for diabetic neuropathy? *Lancet Diabetes Endocrinol* 2014; 2: 607–609.

18. Malik RA. Wherefore art thou, o treatment for diabetic neuropathy? *Int Rev Neurobiol* 2016; 127: 287–317.

19. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005; 352: 341–350.

20. Oellgaard J, Gaede P, Rossing P, et al. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised STENO-2 study. *Diabetologia* 2018; 61: 1724–1733.

21. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; 358: 580–591.

22. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383–393.

23. Ishibashi F, Taniguchi M, Kosaka A, et al. Improvement in neuropathy outcomes with normalizing HbA1c in patients with type 2 diabetes. *Diabetes Care*. Epub ahead of print 19 November 2018. DOI: 10.2337/dc18-1560.

24. Tavakoli M, Kallinikos P, Iqbal A, et al. Corneal confocal microscopy detects improvement in corneal nerve morphology with an improvement in risk factors for diabetic neuropathy. *Diabet Med* 2011; 28: 1261–1267.

25. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care* 2006; 29: 1294–1299.

26. Malik RA, Williamson S, Abbott C, et al. Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; 352: 1978–1981.

27. Ruggenenti P, Lauria G, Iliiev IP, et al. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the delapril and manidipine for nephroprotection in diabetes (DEMAND) randomized clinical trial. *Hypertension* 2011; 58: 776–783.

28. Nielsen SF and Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. *Lancet Diabetes Endocrinol* 2014; 2: 894–900.

29. Davis TM, Yeap BB, Davis WA, et al. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologica* 2008; 51: 562–566.

30. Nassaji M, Ghorbani R and Saboori Shkofe H. Previous atorvastatin treatment and risk of diabetic foot infection in adult patients: a case-control study. *Wounds* 2017; 29: 196–201.

31. Rajamani K, Colman PG, Li LP, et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; 373: 1780–1788.

32. Sohn MW, Meadows JL, Oh EH, et al. Statin use and lower extremity amputation risk in nonelderly diabetic patients. *J Vasc Surg* 2016; 64: 1723–1724.

33. Fox JD, Baquerizo-Nole KL, Macquhae F, et al. Statins may be associated with six-week diabetic foot ulcer healing. *Wound Repair Regen* 2016; 24: 454–457.

34. Dhatariya K, Bain SC, Buse JB, et al. The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial. *Diabetes Care* 2018; 41: 2229–2235.

35. Moustafa PE. Liraglutide ameliorated peripheral neuropathy in diabetic rats: involvement of oxidative stress, inflammation and extracellular matrix remodeling. *Diabetes Metab Res Rev* 2018; 146: 173–185.

36. Sango K and Utsunomiya K. Efficacy of glucagon-like peptide-1 mimetics for neural regeneration. *Neural Regen Res* 2018; 146: 2235.

37. Tsukamoto M, Niimi N, Sango K, et al. Neurotrophic and neuroprotective properties
of exendin-4 in adult rat dorsal root ganglion neurons: involvement of insulin and RhoA. *Histocherm Cell Biol* 2015; 144: 249–259.

38. Sorensen L, Molyneaux L and Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes Care* 2006; 29: 883–887.

39. Vlckova-Moravcova E, Bednarik J, Belobradkova J, et al. Small-fibre involvement in diabetic patients with neuropathic foot pain. *Diabet Med* 2008; 25: 692–699.

40. Quattrini C, Tavakoli M, Jeziorska M, et al. Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes* 2007; 56: 2148–2154.

41. Van Acker K, Bouhassira D, De Bacquer D, et al. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* 2009; 35: 206–213.

42. Bohlega S, Alsaadi T, Amir A, et al. Guidelines for the pharmacological treatment of peripheral neuropathic pain: expert panel recommendations for the middle East region. *J Int Med Res* 2010; 38: 295–317.

43. DaCosta DiBonaventura M, Cappelleri JC and Joshi AV. A longitudinal assessment of painful diabetic peripheral neuropathy on health status, productivity, and health care utilization and cost. *Pain Med* 2011; 12: 118–126.

44. Abbott CA, Malik RA, van Ross ER, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011; 34: 2220–2224.

45. Jambart S, Ammache Z, Haddad F, et al. Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. *J Int Med Res* 2011; 39: 366–377.

46. Davies M, Brophy S, Williams R, et al. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2006; 29: 1518–1522.

47. Ziegler D, Rathmann W, Meisinger C, et al. Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-diabetes and diabetes. The KORA Myocardial Infarction Registry. *Eur J Pain* 2009; 13: 582–587.

48. Jacovides A, Bogoshi M, Distiller LA, et al. An epidemiological study to assess the prevalence of diabetic peripheral neuropathic pain among adults with diabetes attending private and institutional outpatient clinics in South Africa. *J Int Med Res* 2014; 42: 1018–1028.

49. Sadosky A, McDermott AM, Brandenburg NA, et al. A review of the epidemiology of painful diabetic peripheral neuropathy, postherpetic neuralgia, and less commonly studied neuropathic pain conditions. *Pain Pract* 2008; 8: 45–56.

50. Abbott CA, Chaturvedi N, Malik RA, et al. Explanations for the lower rates of diabetic neuropathy in Indian Asians versus Europeans. *Diabetes Care* 2010; 33: 1325–1330.

51. Fadavi H, Tavakoli M, Foden P, et al. Explanations for less small fibre neuropathy in south Asian versus European subjects with type 2 diabetes in the UK. *Diabet Med Metab Res Rev* 2018; 34: e3044.

52. Spallone V, Morganti R, D’Amato C, et al. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med* 2012; 29: 578–585.

53. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain* 2001; 92: 147–157.

54. Krause SJ and Backonja MM. Development of a neuropathic pain questionnaire. *Clin J Pain* 2003; 19: 306–314.

55. Daousi C, MacFarlane IA, Woodward A, et al. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* 2004; 21: 976–982.

56. Ziegler D, Landgraf R, Lobmann R, et al. Painful and painless neuropathies are distinct and largely undiagnosed entities in subjects participating in an educational initiative (PROTECT study). *Diabetes Res Clin Pract* 2018; 139: 147–154.

57. Malik RA, Aldinc E, Chan SP, et al. Perceptions of painful diabetic peripheral neuropathy in South-East Asia: results from patient and physician surveys. *Adv Ther* 2017; 34: 1426–1437.

58. Aslam A, Singh J and Rajbhandari S. Prevalence of painful diabetic neuropathy using the self-completed Leeds assessment of neuropathic symptoms and signs questionnaire in a population with diabetes. *Can J Diabetes* 2015; 39: 285–295.

59. Harris M, Eastman R and Cowie C. Symptoms of sensory neuropathy in adults with NIDDM
in the U.S. population. Diabetes Care 1993; 16: 1446–1452.

60. Smith AG and Singleton JR. Impaired glucose tolerance and neuropathy. Neurologist 2008; 14: 23–29.

61. Alam U, Arul-Devah V, Javed S, et al. Vitamin D and diabetic complications: true or false prophet? Diabetes Ther 2016; 7: 11–26.

62. Shillo P, Selvarajah D, Greig M, et al. Reduced vitamin D levels in painful diabetic peripheral neuropathy. Epub ahead of print 20 September 2018. DOI: 10.1111/dme.13798.

63. Gibbons CH and Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain 2015; 138: 43–52.

64. Spallone V. Might genetics play a role in understanding and treating diabetic polyneuropathy? Diabetes Metab Res Rev 2017; 33.

65. Wadhawan S, Pant S, Golhar R, et al. NaV channel variants in patients with painful and nonpainful peripheral neuropathy. Neurol Genet 2017; 3:e207.

66. Vollert J, Maier C, Attal N, et al. Stratifying patients with peripheral neuropathic pain based on sensory profiles: algorithm and sample size recommendations. Pain 2017; 158: 1446–1455.

67. Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. Pain 2014; 155: 2263–2273.

68. Marshall AG, Lee-Kubli C, Azmi S, et al. Spinal disinhibition in experimental and clinical painful diabetic neuropathy. Diabetes 2017; 66: 1380–1390.

69. Botney M and Fields HL. Amitriptyline potentiates morphine analgesia by a direct action on the central nervous system. Ann Neurol 1983; 13: 160–164.

70. Benbouzid M, Gaveriaux-Ruff C, Yalcin I, et al. Delta-opioid receptors are critical for tricyclic antidepressant treatment of neuropathic allodynia. Biol Psychiatry 2008; 63: 633–636.

71. De Gandarias JM, Echevarria E, Acebes I, et al. Effects of imipramine administration on mu-opioid receptor immunostaining in the rat forebrain. Arzneimittel-Forschung 1998; 48: 717–719.

72. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev 2015; 7: CD008242.
polyneuropathy. Br J Anaesth 2014; 113: 148–156.

85. Schwartz S, Etropolis MS, Shapiro DY, et al. A pooled analysis evaluating the efficacy and tolerability of tapentadol extended release for chronic, painful diabetic peripheral neuropathy. Clin Drug Invest 2015; 35: 95–108.

86. Vadivelu N, Kai A, Maslin B, et al. Tapentadol extended release in the management of peripheral diabetic neuropathic pain. Ther Clin Risk Manag 2015; 11: 95–105.

87. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The “COMBO-DN study”—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 2013; 154: 2616–2625.

88. Bouhassira D, Wilhelm S, Schacht A, et al. Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. Pain 2014; 155: 2171–2179.

89. Boyle J, Eriksson MEV, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012; 35: 2451–2458.

90. Basit A, Basit KA, Fawwad A, et al. Vitamin D for the treatment of painful diabetic neuropathy. BMJ Open Diabetes Res Care 2016; 4: e000148.

91. Alam U and Fawwad A. Improvement in neuropathy specific quality of life in patients with diabetes after vitamin D supplementation. J Diabetes Res 2017; 2017: 7928083.

92. Soedamah-Muthu SS, Chaturvedi N, Witte DR, et al. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care 2008; 31: 1360–1366.

93. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010; 33: 1578–1584.

94. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004; 27: 2942–2947.

95. Suarez GA, Opfer-Gehrking TL, Offord KP, et al. The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology 1999; 52: 523–528.

96. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33: 2285–2293.

97. Martin CL, Albers JW, Pop-Busui R, et al. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37: 31–38.

98. Charles M, Fleischer J, Witte DR, et al. Impact of early detection and treatment of diabetes on the 6-year prevalence of cardiac autonomic neuropathy in people with screen-detected diabetes: ADDITION-Denmark, a cluster-randomised study. Diabetologia 2013; 56: 101–108.

99. Charles M, Ejskjaer N, Witte DR, et al. Prevalence of neuropathy and peripheral arterial disease and the impact of treatment in people with screen-detected type 2 diabetes: the ADDITION-Denmark study. Diabetes Care 2011; 34: 2244–2249.

100. Ziegler D, Schatz H, Conrad F, et al. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). Deutsche Kardiale Autonome Neuropathie. Diabetes Care 1997; 20: 369–373.

101. Pop-Busui R, Stevens MJ, Raffel DM, et al. Effects of triple antioxidant therapy on measures of cardiovascular autonomic neuropathy and on myocardial blood flow in type 1 diabetes: a randomised controlled trial. Diabetologia 2013; 56: 1835–1844.

102. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. Diabetes Care 2010; 33: 434–441.

103. Freeman R, Abuzinadah AR, Gibbons C, et al. Orthostatic hypotension: JACC state-of-the-art review. J Am Coll Cardiol 2018; 72: 1294–1309.

104. Gibbons CH, Schmidt P, Biaggioni I, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol 2017; 264: 1567–1582.

105. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med 2008; 358: 615–624.
106. Kaufmann H. Droxidopa for symptomatic neurogenic orthostatic hypotension: what can we learn? Clin Auton Res 2017; 27: 1–3.

107. Parkman HP, Hasler WL, Fisher RS, et al. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004; 127: 1592–1622.

108. Kumar M, Chapman A, Javed S, et al. The investigation and treatment of diabetic gastroparesis. Clin Ther 2018; 40: 850–861.

109. Sommers T, Mitsuhashi S, Singh P, et al. Prevalence of chronic constipation and chronic diarrhea in diabetic individuals in the United States. Am J Gastroenterol. 2019; 114: 135-142.

110. Borbely YM, Osterwalder A, Kroll D, et al. Diarrhea after bariatric procedures: diagnosis and therapy. World J Gastroenterol 2017; 23: 4689–4700.

111. Murao S and Hosokawa H. Serotonin 5-HT3 receptor antagonist for treatment of severe diabetic diarrhea. Diabetes Care 2010; 33: e38.

112. Ogbonnaya KI and Arem R. Diabetic diarrhea. Pathophysiology, diagnosis, and management. Arch Intern Med 1990; 150: 262–267.

113. Freeman R. Autonomic peripheral neuropathy. Lancet 2005; 365: 1259–1270.

114. Yuan Z, Tang Z, He C, et al. Diabetic cystopathy: a review. J Diabetes 2015; 7: 442–447.

115. Gibbons CH, Illigens BM, Wang N, et al. Quantification of sweat gland innervation: a clinical-pathologic correlation. Neurology 2009; 72: 1479–1486.

116. Gibbons CH, Illigens BM, Wang N, et al. Quantification of sudomotor innervation: a comparison of three methods. Muscle Nerve 2010; 42: 112–119.

117. Ponirakis G, Fadavi H, Petropoulos IN, et al. Automated quantification of neuropad improves its diagnostic ability in patients with diabetic neuropathy. J Diabetes Res 2015; 2015: 847854.

118. Ponirakis G, Petropoulos IN, Fadavi H, et al. The diagnostic accuracy of neuropad for assessing large and small fibre diabetic neuropathy. Diabet Med 2014; 31: 1673–1680.