Diabetic neuropathy: Beyond the basics

Karl Guttormsen, Paul Chadwick

Diabetic peripheral neuropathy is one of the most common complications of diabetes and is a major risk factor for a cascade of severe complications, including ulceration, amputation and death. Neuropathy can broadly be classified into three categories: sensory, autonomic and motor. This article is an essential guide to the pathology, screening and management of neuropathy. By understanding how to prevent and assess this complication, and when to refer to specialist care, healthcare professionals can reduce the risk of the devastating complications associated with it.

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Article points

1. Diabetic neuropathy is one of the most common complications of diabetes and a major risk factor for morbidity and mortality.
2. It may result in sensory loss, pain or motor dysfunction, or it may comprise a combination of some or all of these presentations.
3. If sensory neuropathy or loss of protective sensation is suspected, referral to a specialist podiatry service is important, in order to prevent ulceration and its potentially devastating consequences.

Key words

- Diabetic foot ulceration
- Diabetic neuropathy
- Loss of protective sensation

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In 2013 there were approximately 2.9 million people in the UK with a diagnosis of diabetes, and by 2025 that figure is predicted to exceed 5 million (NICE, 2015). With this growing pandemic comes a growing cost to our patients, the NHS and society as a whole. The Health and Social Care Information Centre recently published a report showing that the cost of medication alone used to treat diabetes in primary care had risen by 56%, from £513.9 million in 2005 to £803.1 million in 2013 (NHS Digital, 2014). The total cost attributed to treating type 1 and type 2 diabetes in the UK has been estimated at £23.7 billion in 2010, with more than three quarters of this attributable to managing complications (Hex et al, 2012). Given both the financial impact and the effects on our patients, the importance of recognising, diagnosing and managing these complications is vital.

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, affecting up to 50% of people with the condition (Diabetes UK, 2015). It commonly manifests as distal and symmetrical polyneuropathy, and it is a major risk factor for morbidity and mortality (Cameron et al, 2001; Tesfaye and Kempler, 2005). It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes (Boulton et al, 1998).

The exact mechanisms that lead to DPN are not fully understood; however, macrovascular and microvascular changes resulting in reduced perfusion to the nerve or endoneural hypoxia, along with hyperglycaemia, are strongly correlated with it (Cameron et al, 2001; Dobretsov et al 2007; Callaghan et al 2012).

This short article aims to delineate the different types of neuropathy affecting people with diabetes. It is meant to act as an aide-mémoire for the clinician and to challenge some of the preconceptions that may hinder education and patient understanding.

Types of neuropathy

DPN can be classified into three major categories: sensory, autonomic and motor.

Sensory neuropathy

From a clinician's perspective, sensory neuropathy is one of the most devastating complications of nerve dysfunction in the diabetic foot. The

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1. Sensory neuropathy and the inability to detect foot damage is a major contributory factor in more than 80% of diabetic foot ulcers.
2. The Semmes–Weinstein 10 g monofilament test and the 128 MHz tuning fork vibration perception test are recommended together to assess for sensory neuropathy and loss of protective sensation (LOPS).
3. In addition to diagnosing sensory neuropathy/LOPS, clinicians must be confident in explaining the consequences to their patients.

inability to feel pain, temperature or pressure in the foot is a major contributory factor in more than 80% of diabetic foot ulcers (Reiber et al, 1995). With ulceration preceding amputation in up to 85% of cases (Muller et al, 2002), the effects of neuropathy are far-reaching.

By itself, sensory neuropathy does not inevitably result in ulceration or limb loss, but the interval between the patient's loss of sensation and a diagnosis of sensory neuropathy needs to be as short as possible, in order to prevent these devastating complications from occurring in the future. By understanding how to prevent, assess and manage sensory neuropathy, each healthcare professional who treats people with diabetes can play their part to prevent the catastrophic cascade associated with it.

Testing for sensory neuropathy

A diagnosis of sensory neuropathy is based on clinical assessment and cannot be made based on history alone. If sensory neuropathy is suspected, clinical investigation to exclude non-diabetic causes is essential. The most common non-diabetic causes are alcohol/drug abuse, trauma/surgery, infection, vitamin B12 deficiency and folate malabsorption. Therefore, clinical tests to exclude these causes include serum B12, thyroid function, blood urea nitrogen and serum creatinine (Boulton et al, 1998).

Once other causes have been ruled out, the Semmes–Weinstein 10 g monofilament test has been shown to have >87% sensitivity in detecting sensory neuropathy, with specificity ranging from 68% to 100% (Boulton et al, 2005; Dros et al, 2009). Although the test cannot be used to make a definitive diagnosis, it is used widely in clinical practice as a first-line, pragmatic approach. Nerve conduction studies are the only way to definitively diagnose neuropathy (Boulton et al, 1998; 2005); however, we can confidently diagnose "loss of protective sensation" (LOPS). This may merely require changing the language we use in terms of what we state as a diagnosis; that is, rather than stating that a patient has sensory neuropathy, a diagnosis of LOPS should be made and explained (Boulton et al, 2008).

The 10 g monofilament test has been shown to have a sensitivity of 86% when tested at eight sites, while the 128 MHz tuning fork vibration perception test has an equal sensitivity when tested at only one site: the apex of the hallux (Miranda-Palma et al, 2005). For this reason, and because the vibration test is an inexpensive, simple, repeatable method, we recommend using the two tests together when assessing LOPS.

Currently, there is no evidence base to determine which sites on the foot should be tested or how often. In clinical practice, however, three to five sites of the foot are commonly regarded as sufficient for monofilament examination. The International Working Group on the Diabetic Foot (2015) recommends that the appropriate sites for monofilament testing are:

1. The plantar aspect of the first toe (hallux).
2. The plantar aspect of the first metatarsal head.
3. The plantar aspect of the fifth metatarsal head.

Boulton et al (2008) recommend that the appropriate site for the 128 MHz tuning fork test is:

- The distal phalanx of the first toe.

Advice on conducting the monofilament and tuning fork tests is presented in *Figures 1* and *2*.

Both exams should be performed twice at each site. **One** abnormal response to either test is sufficient for a diagnosis of LOPS, while normal responses at each site with both modalities are sufficient to exclude it.

Merely testing for LOPS/sensory neuropathy is not enough; clinicians must be confident in explaining the consequences to their patients. Simply telling a patient that they have LOPS/neuropathy will not necessarily help to prevent them from developing a thermal injury, ulcer, shoe rub or even amputation. Explaining what LOPS/neuropathy means, and relating it to the risk of developing a foot ulcer, is vital. The use of real-life examples such as the person who burnt themselves sitting next to the fire or who walked all day with glass in their foot may help patients better understand that risk.

If neuropathy is suspected and a diagnosis of LOPS is made, the patient is at increased risk of developing a diabetic foot ulcer and should be referred to a foot protection team for ongoing monitoring and management (NICE, 2015). Tight glycaemic control, pressure off-loading/

redistribution and robust health education are the only treatment strategies for prevention. If a foot protection team is not available, referral to the local podiatry department may be a reasonable alternative.

Painful neuropathy

Painful DPN/nerve dysfunction may present with symptoms of altered sensation, originating within either the peripheral or the central nervous system. The pain is independent of external stimuli and may be described as one or more of the following: burning, electric shocks, aches, shooting pains, pins and needles (paraesthesia), walking on pebbles or hypersensitivity (allodynia). From a patient's perspective, painful DPN is one of the most distressing presentations of neuropathy and is one of the main contributory factors to their seeking medical attention (Quattrini and Tesfaye, 2003; Tesfaye and Kempler, 2005). Painful DPN is often exacerbated at night, and it typically affects the toes and outer edges of the feet. It may be relieved with activity; this distinction, alongside a thorough vascular assessment, may help differentiate it from vascular rest pain.

Painful DPN may be acute or chronic. Acute DPN is reversible and is a consequence of either poor glycaemic control or rapid improvement in glycaemic control. Once the cause is addressed, resolution may typically be expected within 12 months (Tesfaye et al, 2011). Chronic painful DPN is not reversible, and treatment is difficult and focuses on symptom management. While there is a well-established correlation of glucose control and cardiovascular risk factors with development of the other DPNs, the causes of painful neuropathy are largely unknown (Tesfaye et al, 2011). Chronic pain can have a major impact on a person's quality of life, and depression is common in people with painful DPN (Davies et al, 2006; Tesfaye et al, 2011).

Diagnosing neuropathic pain can be challenging as there are a number of causes that need to be differentiated. The differential diagnosis of foot pain is summarised in *Table 1* (Guttormsen and Haycocks, 2015).

Page points

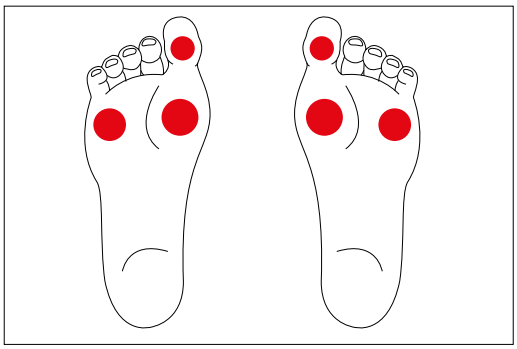
1. If sensory neuropathy is diagnosed, tight glycaemic control, pressure off-loading/redistribution and robust health education are the only treatment strategies to prevent ulceration. Referral to a foot protection team or the local podiatry department is advised.
2. Painful neuropathy is independent of external stimuli, is often exacerbated at night and typically affects the toes and outer edges of the feet.
3. Chronic pain can have a major impact on a person's quality of life, and depression is common in people with painful neuropathy.

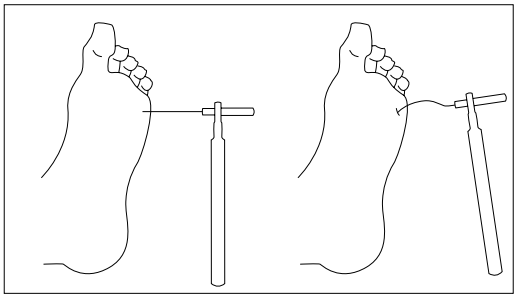
Sensory examination should be carried out in a quiet and relaxed setting. First apply the monofilament to the patient's hand, elbow or forehead, so that they know what to expect.

Test procedure:

- Apply the monofilament to the three sites shown, on both feet. The patient must not be able to see whether or where the examiner applies the filament.
- Where applicable, apply the filament along the perimeter of, not on, an ulcer site, callus, scar or necrotic tissue.
- Touch the monofilament perpendicular to the skin surface, applying sufficient force to cause it to bend or buckle, as shown.
- The total duration of the approach, including skin contact and removal of the filament, should be approximately 2 seconds.
- Do not allow the filament to slide across the skin or make repetitive contact at the test site.
- Press the filament to the skin and ask the patient whether they feel the pressure applied and next where they feel the pressure (left foot/right foot).
- Repeat this application twice at the same site, but alternate this with at least one "mock" application, in which the filament is not applied (three questions per site in total). Encourage patients during testing by giving positive feedback.

Protective sensation is present at each site if the patient correctly answers two out of three applications. Protective sensation is absent with two out of three incorrect answers – the patient is then considered to be at risk of ulceration.





Note: Be aware of the possible loss of buckling force if the monofilament is used for too long a period of time.

Figure 1. Advice on conducting the 10 g monofilament test (International Working Group on the Diabetic Foot, 2015).

Table 1. Differential diagnosis of foot pain (Guttormsen and Haycocks, 2015).

	Neuropathic pain	Ischaemic rest pain	Intermittent claudication	Musculoskeletal: plantar fasciitis
Type and where the pain is	Sharp stabbing or burning pain around the toes	Severe unremitting tooth ache type pain around the toes, at the back of the leg or at an ulcer or gangrenous site	Cramping calf pain predominantly, but can present atypically in the posterior thigh or buttock	Sharp twingeing pain in the plantar aspect of the foot, particularly at the insertion of a tendon, ligament or fascia
What makes it worse	Night-time	Present all the time, but often worse when lying down	After walking a set distance (e.g. 100 m); this is a repeatable pain	First thing in the morning or upon commencing activity (as tendons are cold and inelastic)
What makes it better	Walking	Dangling legs out of bed (gravity helps dependent blood flow)	Eases after <10 minutes' rest, but will reoccur after walking the same set distance	Stretches, as when tendons have warmed up the symptoms ease
What to do	Refer for management to appropriate practitioner (e.g. multidisciplinary foot care team or GP)	If present, this is a clinical emergency and an urgent referral to a vascular surgeon should be made	Referral for further vascular examination (e.g. ankle–brachial pressure index assessment or arterial duplex)	Identification of the cause is the key to providing treatment and referral to a podiatrist specialising in musculoskeletal assessment is indicated

Treatment of painful DPN is complex and can be frustrating (Tesfaye and Kempler, 2005). NICE (2013) has developed a treatment pathway for neuropathic pain, and this should be followed when treating in the non-specialist setting.

Autonomic neuropathy

Diabetic autonomic neuropathy (DAN) can involve every system in the body and is an independent risk factor for mortality, substantial morbidity and risk of developing a diabetic foot ulcer (Vinik et al, 2003; Boulton et al, 2005). Its main presentations include tachycardia, orthostatic hypotension, exercise intolerance, gastroparesis, constipation, impaired neurovascular function, erectile dysfunction, sudomotor dysfunction and hypoglycaemic autonomic failure ("brittle diabetes"; Vinik et al, 2003). The latter can be very unsettling for patients, as it means they lose the awareness that they are becoming hypoglycaemic.

The sensory exam should be carried out in a quiet and relaxed setting. First, apply the tuning fork to the patient's wrist, elbow or clavicle so that they know what to expect. The patient must not be able to see whether or where the examiner applies the tuning fork.

Test procedure:

- Apply the tuning fork to a bony part on the dorsal side of the distal phalanx of the first toe, as shown. The tuning fork should be applied perpendicularly with constant pressure.
- Repeat this application twice, but alternate this with at least one "mock" application, in which the tuning fork is not vibrating.

Patients are "at risk of ulceration" if they have two incorrect answers out of three.

- If the patient is unable to sense the vibrations on the big toe, the test is repeated more proximally (at the malleolus and tibial tuberositas).

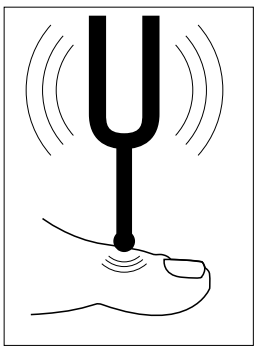


Figure 2. Advice on conducting the 128 MHz tuning fork test (International Working Group on the Diabetic Foot, 2015).

The most clinically significant presentation, however, is cardiovascular autonomic neuropathy, as this can lead to silent myocardial infarctions (Vinik et al, 2003; Boulton et al, 2005).

In the feet, dilated dorsal veins, pounding pulses and anhidrosis (inability to sweat) may all be indicators of DAN, and care should be taken to assess for these signs. There is no formal test and the diagnosis is usually clinical, although the Neuropad (Trigocare International, Wiehl–Drabenderhöhe, Germany) can detect changes in skin sweat reflex (Papanas et al, 2013).

It is also important to recognise that postural hypotension (a drop in systolic blood pressure of >30 mmHg when changing from a supine to a standing position, without any increase in heart rate) can be a disabling symptom of DAN, especially if accompanied by postural syncope (Said, 2007).

Owing to the wide systemic effects, presentations of DAN should trigger referral to a GP or specialist diabetes team for further assessment and management of symptoms (Boulton et al, 2005).

Motor neuropathy

Diabetic peripheral motor neuropathy often receives very little attention (Garces-Sanchez et al, 2011), possibly because motor neuropathy is an umbrella term to include a multitude of disorders. It affects the nerves that control movement and may be symmetrical or asymmetrical (Said, 2007; Garces-Sanchez et al, 2011). It presents as muscle weakness, wasting, cramps and/or twitching. These symptoms may hinder walking, increase the risk of falls and, if in the hands, cause difficulties with tasks involving fine motor skills. When coupled with glycation of tendon proteins (as a result of sustained hyperglycaemia), it may lead to a high arch (pes cavus) foot type, with wasting of the lumbricals (intrinsic muscles within the foot) and clawing of the toes, thus predisposing the patient to developing a foot ulcer. Patients may often have hand involvement, and the hands should be inspected for Dupuytren's, other contracture and/or a positive prayer sign (*Figure 3*).

If motor neuropathy is suspected, referral to specialist services (e.g. the podiatry musculoskeletal [biomechanics] department or an orthotist) is essential, as they may be able to help reduce the risks of foot ulceration associated with the condition by making orthoses, footwear or splints.

Charcot neuroarthropathy

Charcot neuroarthropathy (CN) is such a devastating complication of neuropathy that it must be discussed in conjunction with it. CN is a condition of neuropathy not exclusive to diabetes. Disorganisation of bone repair in undetected fractures or trauma/ulceration may result in excessive bone reabsorption and ineffectual bone deposition, leading to an altered foot shape that predisposes to ulceration and may also result in the need for amputation (*Figure 4*).

In a hot (>2°C hotter than the contralateral foot; however, be mindful that bilateral CN is also possible), red (erythematous), swollen (oedematous) neuropathic foot, this devastating condition should always be suspected and needs to be ruled out, especially if the skin is intact. Exclusion should be based on elimination of other causes; investigations include plain film x-ray (however, x-ray is insensitive to detect early CN), MRI, bloods (C-reactive

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1. Autonomic neuropathy can affect all systems in the body, including cardiovascular, gastrointestinal and neurovascular function.
2. Owing to the wide systemic effects, presentations of autonomic neuropathy should trigger referral to a GP or specialist diabetes team for further assessment and management of symptoms.
3. Motor neuropathy presents as muscle weakness, wasting, cramps and/or twitching, and it should trigger referral to specialist services to reduce the associated risk of foot ulceration.
4. Charcot neuroarthropathy is a clinical emergency that requires urgent referral to a specialist team if suspected.

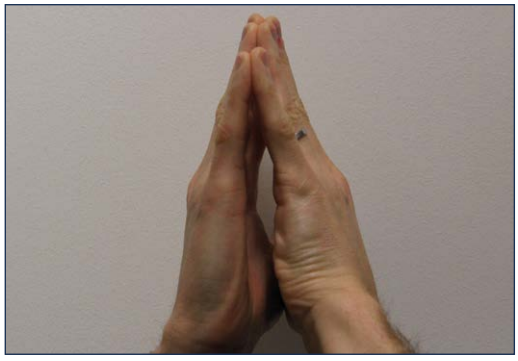

Figure 3. Positive prayer sign. Inability to press the palms together is a sign of motor neuropathy.

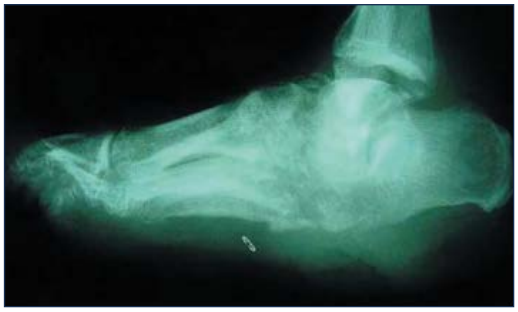

Figure 4. An x-ray of a Charcot foot. Note the collapse and destruction of the bones of the mid-foot, resulting in the classic "rocker-bottom" sole. Reproduced from Al Mousa et al, 2011.

"Diabetic peripheral neuropathy is linked to reduced quality of life and an increased risk of mortality and substantial morbidity."

protein, erythrocyte sedimentation rate and full blood count). First-aid treatment of the condition is to encourage complete non-weight-bearing until assessment by a specialist team for confirmation of the diagnosis can take place; referral should be initiated within one working day (NICE, 2015). The specialist team will encourage non-weight-bearing and may utilise non-removable, below-knee casting in order to achieve this. If non-removable casting is contraindicated, crutches, wheelchairs or removable devices may be used.

Summary

DPN may present as a variety of nervous disorders. It may result in sensory loss, pain originating from the peripheral or central nervous system, or it may affect the autonomic or motor nerves. DPN often comprises a combination of some or all of these presentations. It is linked to reduced quality of life and an increased risk of mortality and substantial morbidity. Development of DPN is strongly correlated with hyperglycaemia and reduced peripheral circulation; as such, tight glycaemic control and cardiovascular risk management is needed in all people with suspected DPN.

When to refer

If sensory neuropathy/LOPS is suspected, referral to a specialist podiatry service may be of benefit. If painful DPN is suspected, NICE (2013) guidance should be followed and, if it cannot be controlled locally, referral to a specialist diabetes centre should be considered. If autonomic neuropathy is suspected, the patient should be referred to their GP or specialist diabetes clinic for further assessment and management of symptoms. Patients with motor neuropathies may benefit from orthoses, footwear or splints, and onward referral for this is needed.

Charcot neuroarthropathy is devastating, limb-threatening and a clinical emergency. If it is suspected, the patient should be encouraged to bear no weight, and referral onwards to a specialist knowledgeable in the condition is vital. ■

Al Mousa M, Al-Arda M, Ajlouni J, Younes N (2011) Clinical factors associated with Charcot foot. *The Diabetic Foot Journal* **14**: 124–9

Boulton AJ, Gries FA, Jervell JA (1998) Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* **15**: 508–14

Boulton AJ, Vinik AI, Arezzo JC et al (2005) Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* **28**: 956–62

Boulton AJ, Armstrong DG, Albert SF et al (2008) Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* **31**: 1679–85

Callaghan BC, Little AA, Feldman EL, Hughes RA (2012) Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* **2012**: CD007543

Cameron NE, Eaton SE, Cotter MA, Tesfaye S (2001) Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* **44**: 1973–88

Davies M, Brophy S, Williams R, Taylor A (2006) The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* **29**: 1518–22

Diabetes UK (2015) *Facts and Stats*. DUK, London. Available at: http://bit.ly/1RINq4f (accessed 08.12.16)

Dobretsov M, Romanovsky D, Stimers JR (2007) Early diabetic neuropathy: triggers and mechanisms. *World J Gastroenterol* **13**: 175–91

Dros J, Wewerinke A, Bindels PJ, van Weert HC (2009) Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Ann Fam Med* **7**: 555–8

Garces-Sanchez M, Laughlin RS, Dyck PJ et al (2011) Painless diabetic motor neuropathy: a variant of diabetic lumbosacral radiculoplexus neuropathy? *Ann Neurol* **69**: 1043–54

Guttormsen K, Haycocks S (2015) In the consultation room: diabetic foot assessment. *Diabetes & Primary Care* **17**: 285–7

Hex N, Bartlett C, Wright D et al (2012) Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* **29**: 855–62

International Working Group on the Diabetic Foot (2015) *Prevention and management of foot problems in diabetes: A Summary Guidance for daily practice 2015, based on the IWGDF Guidance documents*. IWGGDF, Brussels. Available at: http://bit.ly/2h5DGoG (accessed 08.12.16)

Miranda-Palma B, Sosenko JM, Bowker JH et al (2005) A comparison of the monofilament with other testing modalities for foot ulcer susceptibility. *Diabetes Res Clin Pract* **70**: 8–12

Muller IS, de Grauw WJ, van Gerwen WH et al (2002) Foot ulceration and lower limb amputation in type 2 diabetic patients in Dutch primary health care. *Diabetes Care* **25**: 570–4

NHS Digital (2014) *Prescribing for Diabetes, England – 2005–06 to 2013–14*. NHS Digital, Leeds. Available at: http://bit.ly/2hdbX6i (accessed 08.12.16)

NICE (2013) *Neuropathic pain in adults: pharmacological management in non-specialist settings* (CG173). NICE, London. Available at: www.nice.org.uk/guidance/CG173 (accessed 08.12.16)

NICE (2015) *Diabetic foot problems: prevention and management* (NG19). NICE, London. Available at: www.nice.org.uk/guidance/ng19 (accessed 08.12.16)

Papanas N, Boulton AJ, Malik RA et al (2013) A simple new non-invasive sweat indicator test for the diagnosis of diabetic neuropathy. *Diabet Med* **30**: 525–34

Quattrini C, Tesfaye S (2003) Understanding the impact of painful diabetic neuropathy. *Diabetes Metab Res Rev* **19**(Suppl 1): 2–8

Reiber GE, Boyko EJ, Smith DG (1995) Lower extremity foot ulcers and amputations in diabetes. In: *Diabetes in America* (2nd edition). National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA

Said G (2007) Diabetic neuropathy – a review. *Nat Clin Pract Neurol* **3**: 331–40

Tesfaye S, Kempler P (2005) Painful diabetic neuropathy. *Diabetologia* **48**: 805–7

Tesfaye S, Vileikyte L, Rayman G et al (2011) Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab Res Rev* **27**: 629–38

Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. *Diabetes Care* **26**: 1553–79