




REVIEW

# An update on the diagnosis and treatment of diabetic somatic and autonomic neuropathy [version 1; referees: 3 approved]

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**Abstract**



Diabetic peripheral neuropathy (DPN) is the most common chronic complication of diabetes. It poses a significant challenge for clinicians as it is often diagnosed late when patients present with advanced consequences such as foot ulceration. Autonomic neuropathy (AN) is also a frequent and under-diagnosed complication unless it is overtly symptomatic. Both somatic and autonomic neuropathy are associated with increased mortality. Multiple clinical trials have failed because of limited efficacy in advanced disease, inadequate trial duration, lack of effective surrogate end-points and a lack of deterioration in the placebo arm in clinical trials of DPN. Multifactorial risk factor reduction, targeting glycaemia, blood pressure and lipids can reduce the progression of DPN and AN. Treatment of painful DPN reduces painful symptoms by about 50% at best, but there is limited efficacy with any single agent. This reflects the complex aetiology of painful DPN and argues for improved clinical phenotyping with the use of targeted therapy, taking into account co-morbid conditions such as anxiety, depression and sleep disturbance.

**Keywords**

diabetes mellitus, peripheral neuropathy, autonomic neuropathy

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## Diagnosing diabetic peripheral neuropathy: too little too late

The early diagnosis and monitoring of diabetic peripheral neuropathy (DPN) are recommended by both the Toronto consensus<sup>1</sup> and the more recent American Diabetes Association (ADA) position statement on DPN<sup>2</sup>. They recommend the presence of at least one symptom or sign of neuropathy and abnormal neurophysiology for the diagnosis of DPN. Symptom questionnaires, composite neurological scores and quantitative sensory testing (QST) may be used to diagnose DPN (Table 1). The neuropathy disability score<sup>3</sup>, a composite measure of neurological deficits (based on Achilles tendon reflexes, 120-Hz vibration, temperature and pin-prick sensation); Toronto Clinical Neuropathy Score<sup>4</sup>; and the Michigan Neuropathy Screening Instrument<sup>5</sup> are validated neurological scores of clinical DPN. Although these tests are adequate tools to screen for DPN, they lack the sensitivity to assess change in clinical trials of relatively short duration (12–24 months). Yet they continue to be advocated as measures of efficacy, despite serial failure to show benefits in clinical trials of DPN.

QST<sup>6</sup> is a painless, non-invasive means to diagnose small and large fibre dysfunction and is based on impaired thermal, pain and vibration perception, respectively (Table 1). Elevated vibration perception threshold is a risk factor for foot ulceration and lower-extremity amputation<sup>7</sup> but is a subjective test<sup>8</sup>. Light touch can be assessed by using the 10-g monofilament and is commonly advocated as a screening tool for DPN, although it can only detect advanced neuropathy<sup>9</sup> and those at increased risk of amputation<sup>10</sup>. Diagnosing established DPN is akin to ‘closing the stable door after the horse has bolted’.

Nerve conduction studies assess large fibre function and are currently advocated as the gold standard for a definite diagnosis of DPN<sup>11</sup>. The typical electrophysiological findings in DPN are reduced amplitude of the compound muscle action potential, slower nerve conduction velocity, prolonged F-wave latency

and an altered H-reflex. They are particularly useful for differentiating from other or concomitant neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP)<sup>12</sup>. They are also advocated as a primary end-point to measure therapeutic effect but have equally failed in the majority of clinical trials of DPN<sup>13</sup>.

Thus, several caveats ought to be carefully considered when these tests are employed to assess change over time and the response to therapies. Although composite scores and QST are resourceful methods to assess neuropathy, they have poor sensitivity and reproducibility<sup>14</sup> and low histopathological specificity<sup>15</sup>. They may be of value in large longitudinal cohort studies as opposed to individual patients or relatively small phase III clinical trials of short duration<sup>14</sup>. Nerve conduction studies cannot assess small fibre neuropathy and have poor inter-rater reproducibility<sup>16</sup>, making multi-centre trials difficult<sup>17</sup>. Indeed, these measures have consistently failed to show meaningful improvements in clinical trials of neuropathy<sup>18–20</sup>.

Intra-epidermal nerve density (IENFD) evaluation in skin biopsy offers an objective and more reproducible means to assess small nerve fibre pathology<sup>21</sup>. IENFD is reduced in pre-diabetes<sup>22</sup>, predicts incident neuropathy<sup>23</sup> and improves with lifestyle intervention<sup>24</sup>. Unlike neurophysiology, skin biopsy is not confounded by height and weight, although a gender- and age-dependent decline has been reported<sup>21</sup>. There are published guidelines on the use of skin biopsy to diagnose DPN<sup>25</sup>. However, wider adoption of skin biopsy is limited by cost, the need for a dedicated processing and assessment facility, and the risk of bleeding and infection following the procedure. Corneal confocal microscopy (CCM) is a powerful, non-invasive ophthalmic imaging end-point for DPN and other neuropathies<sup>26</sup>. CCM can be used to quantify small fibre pathology with high reproducibility<sup>27</sup>. Corneal c-fibres form the sub-basal nerve plexus and are highly metabolically demanding<sup>28</sup> and hence vulnerable even to transient and minor metabolic perturbation<sup>22</sup>. Recent

**Table 1. Common tests for the assessment of neuropathy.**

Type of nerve	Investigation	Advantages and disadvantages
Large fibre	Nerve conduction studies	Gold standard Sensitive, specific, and reproducible and easily standardised Must be done by trained professional
Large and small fibres	Neuropathy disability score	Good predictor for risk of ulceration Subjective Does not detect sub-clinical large fibre damage
Small fibre	Quantitative sensory testing	Reproducible and reliable Subjective
	Skin biopsy	Gold standard for small fibre testing Reliable and reproducible Invasive procedure which needs specialised laboratory service
	Corneal confocal microscopy	Rapid, reproducible, non-invasive Detects small fibre damage and tracks worsening and improvement in small phase 2b clinical trials Requires training to perform

studies have established CCM values for the diagnosis<sup>29–31</sup> and prediction<sup>32,33</sup> of DPN on the basis of corneal nerve fibre density and length<sup>34–37</sup>. CCM has also shown corneal nerve regeneration in clinical trials before change in other US Food and Drug Administration (FDA)-accepted end-points (for example, neurophysiology and skin biopsy), a finding which has important implications for clinical trial design<sup>13</sup>.

### Disease modification for diabetic neuropathy

In the 2017 ADA position statement on diabetic neuropathy, early recognition of DPN even in pre-diabetes is recommended<sup>2,38,39</sup>. There are no FDA-approved disease-modifying treatments for the management of DPN, and improved glycaemic control to prevent progression forms the mainstay of treatment. In type 1 diabetes mellitus (T1DM), improved glycaemic control can prevent the development and delay the progression of neuropathy<sup>40</sup>. However, in T2DM, there is limited evidence that improved glycaemic control can slow down the progression of neuropathy<sup>41–43</sup>. The EURODIAB IDDM (European Diabetes Centers Study of Complications in Patients with Insulin-dependent Diabetes Mellitus), which evaluated over 3000 patients with T1DM for a duration of 7 years, identified poor glycaemic control, elevated low-density lipoprotein (LDL) cholesterol and triglycerides, hypertension, obesity and smoking as risk factors for incident DPN<sup>44</sup>.

In patients with T1DM, treatment with an angiotensin-converting enzyme (ACE) inhibitor<sup>45</sup> or in combination with a calcium channel blocker<sup>46</sup> has been shown to improve DPN in randomised placebo-controlled trials<sup>47,48</sup>. Statins and fibrates have also been shown to prevent the development of DPN<sup>49,50</sup> and have been associated with reduced diabetic foot infection<sup>51</sup> and lower-extremity amputation<sup>52,53</sup> and increased rate of foot ulcer healing<sup>54</sup>. Recent experimental studies advocate the use of

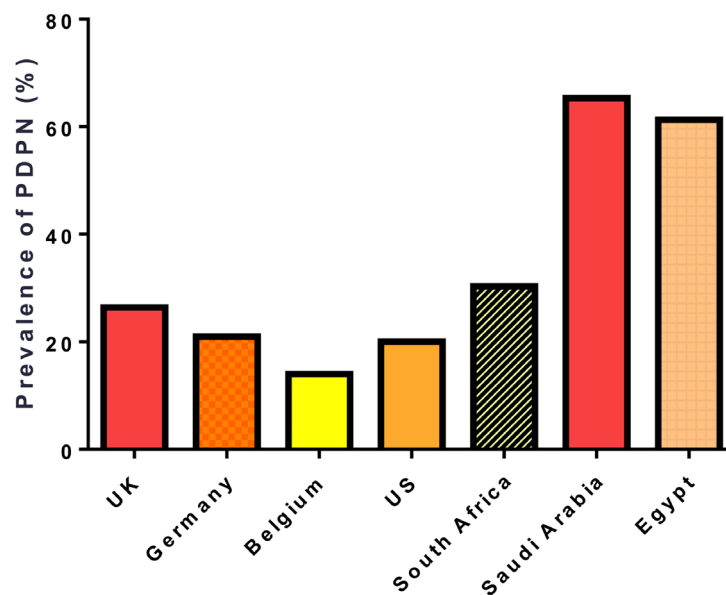
combination therapies targeting several pathogenetic pathways as the most effective approach to the treatment of DPN<sup>55–57</sup>.

### Painful diabetic peripheral neuropathy

#### Diagnosis of painful diabetic peripheral neuropathy

Painful diabetic peripheral neuropathy (PDPN) is a manifestation of small fibre damage<sup>58–60</sup>, characterised by burning pain and tingling with nocturnal exacerbation. It has a significant impact on the patient's quality of life<sup>61–63</sup> and can result in depression, anxiety and sleep disturbance<sup>62</sup>. Estimates of the prevalence of PDPN range from 14.0 to 65.3%<sup>61,64–69</sup> (Figure 1). This difference can be attributed to different populations studied and different diagnostic methods. The prevalence of PDPN is higher in secondary compared with primary care<sup>70</sup> and in patients with T2DM compared with T1DM<sup>61,64,71</sup>. It is important to note that for a large proportion (12.5–61.5%) of patients, PDPN remains undiagnosed<sup>71,72</sup>. They are often unaware that the pain is related to diabetes and do not report it to their clinician<sup>72</sup>. Older age, longer duration of diabetes, and the presence of DPN increase the risk for PDPN<sup>61,64–66,68</sup>; and obesity<sup>61,65,70,71</sup>, low physical activity<sup>24,67</sup>, smoking<sup>64,70</sup>, poor glycaemic control<sup>73,74</sup>, low high-density lipoprotein (HDL) cholesterol<sup>61</sup>, and raised LDL cholesterol, triglycerides and creatinine<sup>67</sup> are independent risk factors for PDPN. Early diagnosis and intervention may be the key, as a study of subjects with pre-diabetes showed that lifestyle intervention reduced neuropathic symptoms and improved small fibre function and structure<sup>24</sup>. Therefore, actively screening patients for PDPN, particularly those at high risk, should allow early identification and symptom relief but may also enable timely disease modification.

There are several screening tests that distinguish nociceptive and neuropathic pain. The most common screening tests for PDPN are the Douleur Neuropathique 4 (DN4) questionnaire<sup>75</sup>, the



**Figure 1.** Prevalence of painful diabetic peripheral neuropathy (PDPN) reported from different countries ranges from 14.0 to 65.3%<sup>61,64–69</sup>.

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale<sup>76</sup> and the Neuropathic Pain Questionnaire (NPQ)<sup>77</sup>. The DN4 is composed of 10 questions (seven symptoms and three neurological deficits), and a score of at least 4 has a high sensitivity (83%) and specificity (90%) for PDPN<sup>78</sup>. The LANSS pain scale is composed of five questions on symptoms and two on neurological deficits, and a score at least 12 has a 85% sensitivity and 80% specificity for PDPN<sup>76</sup>. The NPQ contains 10 questions on quality of pain and two on change in sensation<sup>77</sup> and detects PDPN with 74.7% sensitivity and 77.6% specificity.

### Treatment of painful diabetic peripheral neuropathy

There is no evidence that improvement in glycaemic control improves PDPN; indeed, where rapid and large reductions in HbA1c may precipitate an acute painful neuropathy, the opposite is true<sup>79</sup>. The traditional approach to managing PDPN is to try different therapies until one works (with minimal side effects). However, improved clinical phenotyping and targeting of therapies based on underlying mechanism(s) may result in better outcomes<sup>80</sup>. Detailed phenotyping using QST suggests that in patients with an irritable nociceptor compared with a non-irritable nociceptor phenotype, there is a better response to oxcarbazepine, with a number needed to treat (NNT) of 3.9 compared with 6.9 in those with the non-irritable nociceptor<sup>81</sup>. Identifying abnormalities in rate-dependent depression (RDD), a marker of altered descending inhibitory modulation of pain, may also help to identify patients who will respond optimally to selective norepinephrine reuptake inhibitors for example, duloxetine<sup>82</sup>.

Tricyclic anti-depressants (TCAs) modulate pain and have analgesic efficacy by indirectly modifying the opioid system in the brain and via serotonergic and noradrenaline neuromodulation, amongst other mechanisms<sup>83–85</sup>. Amitriptyline is the most commonly used TCA in PDPN, despite not having a label for its treatment. In a systematic review, Moore *et al.*<sup>86</sup> evaluated 17 studies with 1342 participants and concluded that study quality was modest, and most studies had a high risk of bias due to the small participant numbers<sup>86</sup>. Two serotonin and norepinephrine reuptake inhibitors (SNRIs) are recommended for PDPN: duloxetine and venlafaxine. They exert their effect via inhibiting serotonin and noradrenaline reuptake with potentiation of descending inhibitory pathways<sup>87</sup>. A Cochrane review including eight randomised controlled trials (n = 2728) showed that duloxetine 60 mg daily was superior to placebo, and the NNT was 5<sup>88</sup>. Pregabalin also has FDA approval for PDPN on the basis of a number of randomised controlled trials (RCTs)<sup>89–91</sup>. Snedecor *et al.* undertook a comparative meta-analysis of a number of agents to treat PDPN and found pregabalin to be the most efficacious in reducing Visual Analogue Scale (VAS) pain scores<sup>92</sup>. Duloxetine and pregabalin are both considered first-line therapy by National Institute for Clinical Excellence (NICE) and the 2017 ADA position statement<sup>2,93</sup>. Mirogabalin has also recently shown efficacy and good tolerability in a phase II and two phase III clinical trials in PDPN<sup>94–96</sup>. Tramadol has an opioid plus SNRI effect. A Cochrane Collaboration review found that the efficacy of tramadol in neuropathic pain was determined in small, inadequately sized studies with a risk of bias<sup>97</sup>, although a meta-analysis showed an NNT of 4.4. Tapentadol extended-release

has also shown efficacy in a number of randomised clinical trials and is recommended by the FDA in PDPN<sup>98–101</sup>.

The COMBO-DN (Combination versus Monotherapy of pregabalin and duloxetine in Diabetic Neuropathy) study compared monotherapy with a combination of duloxetine and pregabalin<sup>102</sup>. The pain outcomes between combination (duloxetine 60 mg daily plus pregabalin 300 mg daily) and high-dose monotherapy (duloxetine 120 mg daily or pregabalin 600 mg daily) were comparable<sup>102</sup>. 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<sup>103</sup>. In a double-blind RCT with a parallel-group design, analgesic efficacy was found to be comparable between amitriptyline, duloxetine and pregabalin<sup>104</sup>.

In patients presenting with PDPN, the key is to provide symptom relief, but we would argue that this also represents a window of opportunity for risk factor reduction to limit DPN progression. For symptom relief, pregabalin, gabapentin, duloxetine or amitriptyline can be used first line, and if they are not working or have limited effectiveness because of side effects, then a second-line agent or tramadol can be added in combination (Table 2). Topical therapies such as a glyceryl trinitrate (GTN) spray<sup>105</sup> or patch<sup>106</sup> applied to the feet can be considered and give a favourable NNT of about 4<sup>107,108</sup>. There is an evolving argument that the future management of PDPN will follow a more personalised approach using markers such as RDD<sup>109</sup>, CCM<sup>110</sup> and genomics<sup>111–113</sup> to identify specific mechanisms in patients who will respond better to targeted therapies.

### Cardiac autonomic neuropathy

The Toronto consensus panel defined cardiac autonomic neuropathy (CAN) as the impairment of cardiovascular autonomic control in patients with diabetes mellitus after the exclusion of other causes<sup>114</sup>. CAN occurs in subjects with impaired glucose tolerance (IGT), and abnormal cardiovascular autonomic reflex tests (CARTs) have been reported in up to 7% of patients at diagnosis of T1DM and T2DM<sup>115–117</sup> with the prevalence increasing to 30% (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications, or DCCT/EDIC) after 14 years of T1DM<sup>118,119</sup> and in other studies to 70% after 15 years<sup>120</sup>. CAN is an independent risk factor for mortality<sup>114</sup> and was the strongest risk factor for all-cause mortality in the EURODIAB study (T1DM) and an independent risk factor for mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (T2DM)<sup>121,122</sup>. A meta-analysis of 15 longitudinal studies reported an association between CAN and increased mortality<sup>123</sup>. A meta-analysis of 12 studies identified silent myocardial ischaemia (SMI) in 20% of patients with CAN compared with 10% in those without CAN<sup>117</sup>. CAN is also associated with left ventricular dysfunction<sup>124,125</sup> and independently predicts the progression of diabetic nephropathy<sup>126</sup>.

### Diagnosis of cardiac autonomic neuropathy

Screening for CAN is recommended at diagnosis in patients with T2DM and after 5 years for those with T1DM. Signs and symptoms of CAN should be assessed in patients with microvascular complications and in patients with hypoglycaemia unawareness<sup>2,127</sup>. The diagnosis of CAN includes the documentation

**Table 2. Commonly used therapy for painful diabetic peripheral neuropathy.**

Drug class	Agent	Initial dose	Maintenance dose	Comments and common adverse reactions
Anticonvulsants	Pregabalin <sup>89-92</sup>	25-75 mg three times a day	300-600 mg daily	Adverse events (AEs): dizziness, somnolence, headache and weight gain Approved for the treatment of painful diabetic peripheral neuropathy (DPN) Psychological dependence
	Gabapentin <sup>128,129</sup>	100-300 mg three times a day	900-3600 mg daily	AEs: dizziness, somnolence, ataxia and fatigue Reduce dose if estimated glomerular filtration rate is less than 60 mL/min.
Antidepressants	Duloxetine <sup>88,130-132</sup>	20-30 mg once daily	60-120 mg once daily	Approved for the treatment of painful DPN AEs: somnolence, dizziness, headache, nausea, dry mouth and reduced appetite Avoid in hepatic impairment; avoid with creatinine clearance of less than 30 mL/min.
	Venlafaxine <sup>133,134</sup> Amitriptyline <sup>83,86</sup>	37.5 mg once daily 10-25 mg once daily	75-225 mg once daily 25-100 mg once daily	AEs: nausea, dizziness, constipation, dry mouth, weight loss and constipation AEs: abdominal pain, headaches, dizziness, insomnia, orthostatic hypotension, anorexia, nausea, urinary retention, constipation, blurred vision, mydriasis, weight gain, xerostomia and somnolence
Opioid-like agonists	Tramadol <sup>97</sup>	50 mg four times a day	200-400 mg four times a day	Avoid use in patients older than 60 years of age. AEs: constipation, somnolence, nausea, headache and dizziness
	Tapentadol <sup>98-101</sup>	50-100 mg four to six times per day; can take 700 mg on first day	600 mg daily	AEs: nausea, dizziness, somnolence, constipation, vomiting and headache Potential for addiction, abuse and misuse
Topical therapies	Capsaicin 0.0075% cream <sup>135-138</sup>		Applied three or four times per day	Can be used as an adjunct to oral therapies Use is limited by the frequency of application. Cause denervation, hence may increase risk of foot ulceration
	Lidocaine 5% plaster <sup>92,139</sup>		5% for up to 18 hours per day	AEs: application site reactions; otherwise, has fewer side effects than systemic agents Can be used as an adjunct to oral therapies
	Isosorbide dinitrate <sup>105</sup>		Patch (5 mg) applied at bedtime to the bottom of the feet	AEs: headache. The dose can be halved if this occurs.

of the symptoms and signs (Table 3), but there is a weak correlation between symptoms and autonomic deficits<sup>120,140</sup> and symptoms may be subtle like intermittent palpitations and exercise intolerance. CAN may initially be asymptomatic with the only sign being decreased heart rate variability with deep breathing, which can progress to a resting tachycardia (>100 bpm). In patients who are symptomatic (resting tachycardia with a history of poor glucose control) or where the diagnosis of CAN is very likely, the ADA position statement advises no additional testing<sup>2</sup>. It is important to exclude other causes such as idiopathic orthostatic hypotension (OH), syncope and postural orthostatic tachycardia syndrome (POTS)<sup>141</sup>. CARTs includes heart rate response to deep breathing, standing and the Valsalva manoeuvre.

### Management of autonomic neuropathy

Poor glycaemic control and longer diabetes duration are established risk factors for CAN<sup>42,118,119</sup>. The DCCT showed that intensive glycaemic control in patients with T1DM reduced the development of CAN by 45%<sup>118</sup>. Hypertension, obesity, hyperlipidemia and smoking have also been implicated in the development of CAN<sup>42,117,120,142-144</sup>, and the Steno-2 trial showed that intensified multifactorial treatment in patients with T2DM reduced the risk of CAN progression by 68%<sup>145,146</sup>. There are no FDA-approved disease-modifying treatments to reverse CAN. A small early study found favourable effects of alpha-lipoic acid (ALA) on CAN<sup>147</sup>, however, more recently a study to evaluate triple antioxidant therapy (allopurinol (300 mg once daily), ALA (600 mg twice daily) and nicotinamide (750 mg twice daily)) in patients with mild to moderate CAN found no benefit<sup>148</sup>.

### Orthostatic hypotension

Symptoms of OH occur on standing and include light-headedness, weakness, faintness and syncope. OH is defined by a blood pressure decrease on standing of greater than 20/10 mm Hg (a decrease of greater than 30/15 for those with blood pressure of greater than 150/90) without an appropriate increase in heart rate (<15 bpm)<sup>149</sup>. Treatment of OH involves a review of medication, fluid and salt repletion and encouragement of physical activity and exercise to avoid deconditioning<sup>150,151</sup>. Fludrocortisone is not FDA-approved for OH. It works through sodium retention and constriction of partially denervated blood vessels, but there are concerns over supine hypertension, hypokalaemia, congestive cardiac failure and peripheral oedema<sup>152</sup>. Both midodrine and droxidopa are approved by the FDA for the treatment of symptomatic neurogenic OH<sup>153</sup>.

### Gastroparesis

Gastroparesis is defined as the delayed removal of stomach contents in the absence of a physical obstruction<sup>154</sup>. Gastric emptying should be assessed with scintigraphy 4 hours after food intake of digestible solids at 15-min intervals. Dietary modification with frequent small meals and prokinetics are recommended to increase gastric motility. Metoclopramide is the only FDA-approved drug for the treatment of gastroparesis. However, limited efficacy and the risk of tardive dyskinesia have led the FDA and European Medicines Agency to advise use for a maximum of 5 days. New therapies are being investigated and include motilin receptor agonists, ghrelin receptor agonists, and neurokinin receptor antagonists. Mechanical options for intervention include transpyloric stenting, gastric electrical

**Table 3. Symptoms and signs of diabetic autonomic neuropathy.**

<p><b>Cardiac autonomic neuropathy</b></p> <ul style="list-style-type: none"> <li>• Resting tachycardia or fixed heart rate or both</li> <li>• Loss of circadian rhythm of blood pressure</li> <li>• Increase in nocturnal systolic blood pressure compared with daytime</li> <li>• Orthostatic hypotension</li> <li>• Exercise intolerance</li> <li>• Syncope and light headedness</li> <li>• Intra-operative cardiovascular lability</li> <li>• 'Silent ischemia' and 'painless' myocardial infarction</li> <li>• Arrhythmias</li> </ul> <p><b>Urogenital autonomic neuropathy</b></p> <p>Bladder dysfunction</p> <ul style="list-style-type: none"> <li>• Increase in frequency and urgency particularly during the night</li> <li>• Urinary hesitancy and weak stream</li> <li>• Dribbling of urine and involuntary urination</li> <li>• Urinary incontinence</li> </ul> <p>Sexual dysfunction</p> <ul style="list-style-type: none"> <li>• Male: erectile dysfunction, decreased libido and abnormal ejaculation</li> <li>• Female: decreased sexual desire and arousal, increased pain during intercourse and inadequate lubrication</li> </ul> <p><b>Gastrointestinal autonomic neuropathy</b></p> <ul style="list-style-type: none"> <li>• Nausea/vomiting</li> <li>• Bloating</li> <li>• Inability to eat a full meal</li> <li>• Profuse and watery diarrhoea (nocturnal)</li> <li>• Constipation</li> </ul>
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stimulation, and gastric per-oral endoscopic myotomy; in severe intractable gastroparesis, laparoscopic pyloroplasty or gastrectomy may be options<sup>155</sup>.

### Diabetic diarrhoea

Diabetic diarrhoea is a troublesome gastrointestinal complication which is characterised by watery painless diarrhoea, particularly at night. Other causes of diarrhoea must be excluded, especially therapy with metformin which is often overlooked, and pancreatic exocrine insufficiency (faecal fat of greater than 6 g/72 hours). Pharmacological therapies include anti-diarrhoeal agents (for example, Lomotil or Imodium), antibiotics (tetracycline or metronidazole) to eradicate bacterial overgrowth, somatostatin analogues (octreotide), and selective serotonin 5-hydroxytryptamine type 3 (HT3) receptor antagonists (Ramosetron)<sup>156,157</sup>.

### Bladder disturbance

Bladder dysfunction may occur in up to 50% of patients with diabetes due to urogenital autonomic neuropathy<sup>141</sup>. The earliest manifestation includes increased initiating threshold for the micturition reflex followed by decreased detrusor activity and incomplete bladder emptying. Treatment includes suprapubic pressure, antimuscarinic medication (oxybutynin 5–30 mg 3 times a day; tolterodine 2–8 mg twice a day) for detrusor hyperreflexia and parasympathomimetic medication to reduce detrusor contractility, and intermittent self-catheterisation<sup>2</sup>. It is important to note that none of the medications are FDA-approved for neurogenic bladder and they have approval only for non-neurogenic overactive bladder or other lower urinary tract symptoms.

### Erectile dysfunction


Erectile dysfunction (ED) is a common manifestation in men with diabetes<sup>141</sup>. It may be three times more prevalent, occur 10

to 15 years earlier and is more severe and less responsive to treatment compared with those without diabetes<sup>158</sup>. ED is associated with a higher HbA1c, presence of metabolic syndrome, hypertension, atherogenic dyslipidemia, lower estimated glomerular filtration rate, higher albumin/creatinine ratio and more severe small fibre neuropathy in men with T1DM<sup>159–161</sup>. Sexual dysfunction is also more common in women with diabetes, and 47% of women with diabetic neuropathy had sexual dysfunction<sup>162</sup>. Reduced sexual arousal, decreased lubrication and painful intercourse are the most common symptoms of sexual dysfunction in females with diabetes. Recent recommendations include active smoking cessation (improves ED by about 30%), treatment of those with testosterone deficiency and treatment with statins. 5-phosphodiesterase inhibitors, intra-cavernosal and transurethral prostaglandins, and penile implants can be used for more severe cases<sup>163–165</sup>. There is about a 50% non-responder rate in patients with diabetes as they are less likely to respond to PDE5 inhibitors<sup>166</sup>. Additional modalities such as low-intensity extracorporeal shock wave therapy show promise<sup>167–169</sup> but require larger and better designed clinical trials. There are several explanations for the lack of response<sup>166</sup>, but it may also reflect a more severe neurogenic component to ED in these patients<sup>159</sup>. Indeed, in a recent study, the assessment of nocturnal penile tumescence and rigidity, which reflects predominantly neurogenic abnormalities, had an area under the curve (AUC) of 0.860 in differentiating sildenafil responders from non-responders<sup>170</sup>.

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## References

- Tesfaye S, Boulton AJ, Dyck PJ, *et al.*: **Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments.** *Diabetes Care.* 2010; **33**(10): 2285–93.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pop-Busui R, Boulton AJ, Feldman EL, *et al.*: **Diabetic Neuropathy: A Position Statement by the American Diabetes Association.** *Diabetes Care.* 2017; **40**(1): 136–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Young MJ, Boulton AJ, Macleod AF, *et al.*: **A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population.** *Diabetologia.* 1993; **36**(2): 150–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Perkins BA, Olaleye D, Zinman B, *et al.*: **Simple screening tests for peripheral neuropathy in the diabetes clinic.** *Diabetes Care.* 2001; **24**(2): 250–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Herman WH, Pop-Busui R, Braffett BH, *et al.*: **Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications.** *Diabet Med.* 2012; **29**(7): 937–44.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
-  Maier C, Baron R, Tölle TR, *et al.*: **Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes.** *Pain.* 2010; **150**(3): 439–50.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Young MJ, Breddy JL, Veves A, *et al.*: **The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study.** *Diabetes Care.* 1994; **17**(6): 557–60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Martin CL, Waberski BH, Pop-Busui R, *et al.*: **Vibration perception threshold as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the DCCT/EDIC study.** *Diabetes Care.* 2010; **33**(12): 2635–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Tan LS: **The clinical use of the 10g monofilament and its limitations: a review.** *Diabetes Res Clin Pract.* 2010; **90**(1): 1–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rith-Najarian SJ, Stolusky T, Gohdes DM: **Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria.** *Diabetes Care.* 1992; **15**(10): 1386–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dyck PJ, Overland CJ, Low PA, *et al.*: **Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: CI vs. NPhys trial.** *Muscle Nerve.* 2010; **42**(2): 157–64.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rajabally YA, Stettner M, Kieseier BC, *et al.*: **CIDP and other inflammatory neuropathies in diabetes - diagnosis and management.** *Nat Rev Neurol.* 2017; **13**(10): 599–611.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Malik RA: **Wherefore Art Thou, O Treatment for Diabetic Neuropathy?** *Int Rev Neurobiol.* 2016; **127**: 287–317.  
[PubMed Abstract](#) | [Publisher Full Text](#)





14. Shy ME, Frohman EM, So YT, *et al.*: **Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.** *Neurology.* 2003; **60**(6): 898–904.  
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Løseth S, Stålberg E, Jorde R, *et al.*: **Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies.** *J Neurol.* 2008; **255**(8): 1197–202.  
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Dyck PJ, Norell JE, Tritschler H, *et al.*: **Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity.** *Diabetes Care.* 2007; **30**(10): 2619–25.  
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Malik RA: **Which test for diagnosing early human diabetic neuropathy?** *Diabetes.* 2014; **63**(7): 2206–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Apfel SC: **Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold?** *Int Rev Neurobiol.* 2002; **50**: 393–413.  
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Kennedy WR, Navarro X, Goetz FC, *et al.*: **Effects of pancreatic transplantation on diabetic neuropathy.** *N Engl J Med.* 1990; **322**(15): 1031–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
20. **F** Wahren J, Foyt H, Daniels M, *et al.*: **Long-Acting C-Peptide and Neuropathy in Type 1 Diabetes: A 12-Month Clinical Trial.** *Diabetes Care.* 2016; **39**(4): 596–602.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
21. **F** Bakkens M, Merkiès IS, Lauria G, *et al.*: **Intraepidermal nerve fiber density and its application in sarcoidosis.** *Neurology.* 2009; **73**(14): 1142–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
22. Asghar O, Petropoulos IN, Alam U, *et al.*: **Corneal confocal microscopy detects neuropathy in subjects with impaired glucose tolerance.** *Diabetes Care.* 2014; **37**(9): 2643–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. **F** Løseth S, Stålberg EV, Lindal S, *et al.*: **Small and large fiber neuropathy in those with type 1 and type 2 diabetes: a 5-year follow-up study.** *J Peripher Nerv Syst.* 2016; **21**(1): 15–21.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
24. **F** Smith AG, Russell J, Feldman EL, *et al.*: **Lifestyle intervention for pre-diabetic neuropathy.** *Diabetes Care.* 2006; **29**(6): 1294–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. Lauria G, Cornblath DR, Johansson O, *et al.*: **EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy.** *Eur J Neurol.* 2005; **12**(10): 747–58.  
[PubMed Abstract](#) | [Publisher Full Text](#)
26. 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): 683–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Hertz P, Brill V, Orszag A, *et al.*: **Reproducibility of *in vivo* corneal confocal microscopy as a novel screening test for early diabetic sensorimotor polyneuropathy.** *Diabet Med.* 2011; **28**(10): 1253–60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Kawashima W, Hatake K, Kudo R, *et al.*: **Estimating the Time after Death on the Basis of Corneal Opacity.** *J Forensic Res.* 2014; **6**: 269.  
[Publisher Full Text](#)
29. Perkins BA, Lovblom LE, Brill V, *et al.*: **Corneal confocal microscopy for identification of diabetic sensorimotor polyneuropathy: a pooled multinational consortium study.** *Diabetologia.* 2018; **61**(8): 1856–61.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Petropoulos IN, Alam U, Fadavi H, *et al.*: **Rapid automated diagnosis of diabetic peripheral neuropathy with *in vivo* corneal confocal microscopy.** *Invest Ophthalmol Vis Sci.* 2014; **55**(4): 2071–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Pritchard N, Edwards K, Dehghani C, *et al.*: **Longitudinal assessment of neuropathy in type 1 diabetes using novel ophthalmic markers (LANDMark): study design and baseline characteristics.** *Diabetes Res Clin Pract.* 2014; **104**(2): 248–56.  
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Azmi S, Ferdousi M, Petropoulos IN, *et al.*: **Corneal Confocal Microscopy Identifies Small-Fiber Neuropathy in Subjects With Impaired Glucose Tolerance Who Develop Type 2 Diabetes.** *Diabetes Care.* 2015; **38**(8): 1502–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Pritchard N, Edwards K, Russell AW, *et al.*: **Corneal confocal microscopy predicts 4-year incident peripheral neuropathy in type 1 diabetes.** *Diabetes Care.* 2015; **38**(4): 671–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Tavakoli M, Mitu-Pretorian M, Petropoulos IN, *et al.*: **Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation.** *Diabetes.* 2013; **62**(1): 254–60.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Azmi S, Ferdousi M, Petropoulos IN, *et al.*: **Corneal confocal microscopy shows an improvement in small-fiber neuropathy in subjects with type 1 diabetes on continuous subcutaneous insulin infusion compared with multiple daily injection.** *Diabetes Care.* 2015; **38**(1): e3–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Culver DA, Dahan A, Bajorunas D, *et al.*: **Cibinetide Improves Corneal Nerve Fiber Abundance in Patients With Sarcoidosis-Associated Small Nerve Fiber Loss and Neuropathic Pain.** *Invest Ophthalmol Vis Sci.* 2017; **58**(6): BIO52–BIO60.  
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Lewis EJH, Perkins BA, Lovblom LE, *et al.*: **Effect of omega-3 supplementation on neuropathy in type 1 diabetes: A 12-month pilot trial.** *Neurology.* 2017; **88**(24): 2294–301.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Lee CC, Perkins BA, Kayaniyl S, *et al.*: **Peripheral Neuropathy and Nerve Dysfunction in Individuals at High Risk for Type 2 Diabetes: The PROMISE Cohort.** *Diabetes Care.* 2015; **38**(5): 793–800.  
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Ferdousi M, Azmi S, Petropoulos IN, *et al.*: **Corneal Confocal Microscopy Detects Small Fibre Neuropathy in Patients with Upper Gastrointestinal Cancer and Nerve Regeneration in Chemotherapy Induced Peripheral Neuropathy.** *PLoS One.* 2015; **10**(10): e0139394.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
40. Ang L, Jaiswal M, Martin C, *et al.*: **Glucose control and diabetic neuropathy: lessons from recent large clinical trials.** *Curr Diab Rep.* 2014; **14**(9): 528.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Ohkubo Y, Kishikawa H, Araki E, *et al.*: **Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.** *Diabetes Res Clin Pract.* 1995; **28**(2): 103–17.  
[PubMed Abstract](#) | [Publisher Full Text](#)
42. **F** Ismail-Beigi F, Craven T, Banerji MA, *et al.*: **Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial.** *Lancet.* 2010; **376**(9739): 419–30.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
43. Callaghan BC, Little AA, Feldman EL, *et al.*: **Enhanced glucose control for preventing and treating diabetic neuropathy.** *Cochrane Database Syst Rev.* 2012; (6): CD007543.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Testaye S, Chaturvedi N, Eaton SE, *et al.*: **Vascular risk factors and diabetic neuropathy.** *N Engl J Med.* 2005; **352**(4): 341–50.  
[PubMed Abstract](#) | [Publisher Full Text](#)
45. 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**(9145): 1978–81.  
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Ruggenenti P, Lauria G, Iliov 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**(5): 776–83.  
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Malik RA: **Can diabetic neuropathy be prevented by angiotensin-converting enzyme inhibitors?** *Ann Med.* 2000; **32**(1): 1–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Malik RA, Tomlinson DR: **Angiotensin-converting enzyme inhibitors: are there credible mechanisms for beneficial effects in diabetic neuropathy?** *Int Rev Neurobiol.* 2002; **50**: 415–30.  
[PubMed Abstract](#) | [Publisher Full Text](#)
49. **F** Nielsen SF, Nordestgaard BG: **Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study.** *Lancet Diabetes Endocrinol.* 2014; **2**(11): 894–900.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
50. **F** Davis TM, Yeap BB, Davis WA, *et al.*: **Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study.** *Diabetologia.* 2008; **51**(4): 562–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. Nassaji M, Ghorbani R, Saboori Shkotte H: **Previous Atorvastatin Treatment and Risk of Diabetic Foot Infection in Adult Patients: A Case-control Study.** *Wounds.* 2017; **29**(7): 196–201.  
[PubMed Abstract](#)
52. 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**(9677): 1780–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Sohn MW, Meadows JL, Oh EH, *et al.*: **Statin use and lower extremity amputation risk in nonelderly diabetic patients.** *J Vasc Surg.* 2013; **58**(6): 1578–1585.e1.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. **F** Fox JD, Baquerizo-Nole KL, Macquhrie F, *et al.*: **Statins may be associated with six-week diabetic foot ulcer healing.** *Wound Repair Regen.* 2016; **24**(2): 454–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Davidson EP, Coppey LJ, Shevalye H, *et al.*: **Effect of Dietary Content of Menhaden Oil with or without Salsalate on Neuropathic Endpoints in High-Fat-Fed/Low-Dose Streptozotocin-Treated Sprague Dawley Rats.** *J Diabetes Res.* 2018; **2018**: 2967127.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

56. **F** Davidson EP, Coppey LJ, Shevalye H, *et al.*: **Impaired Corneal Sensation and Nerve Loss in a Type 2 Rat Model of Chronic Diabetes Is Reversible With Combination Therapy of Menhaden Oil,  $\alpha$ -Lipoic Acid, and Enalapril.** *Cornea*. 2017; **36**(6): 725–31.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
57. **F** Davidson EP, Coppey LJ, Shevalye H, *et al.*: **Vascular and Neural Complications in Type 2 Diabetic Rats: Improvement by Sacubitril/Valsartan Greater Than Valsartan Alone.** *Diabetes*. 2018; **67**(8): 1616–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. Sorensen L, Molyneux L, Yue DK: **The relationship among pain, sensory loss, and small nerve fibers in diabetes.** *Diabetes Care*. 2006; **29**(4): 883–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Vickova-Moravcova E, Bednarik J, Belobradkova J, *et al.*: **Small-fibre involvement in diabetic patients with neuropathic foot pain.** *Diabet Med*. 2008; **25**(6): 692–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
60. Quattrini C, Tavakoli M, Jeziorska M, *et al.*: **Surrogate markers of small fiber damage in human diabetic neuropathy.** *Diabetes*. 2007; **56**(8): 2148–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
61. 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**(3): 206–13.  
[PubMed Abstract](#) | [Publisher Full Text](#)
62. 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**(2): 295–317.  
[PubMed Abstract](#) | [Publisher Full Text](#)
63. daCosta DiBonaventura M, Cappelleri JC, Joshi AV: **A longitudinal assessment of painful diabetic peripheral neuropathy on health status, productivity, and health care utilization and cost.** *Pain Med*. 2011; **12**(1): 118–26.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. 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**(10): 2220–4.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. 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**(2): 366–77.  
[PubMed Abstract](#) | [Publisher Full Text](#)
66. 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**(7): 1518–22.  
[PubMed Abstract](#) | [Publisher Full Text](#)
67. 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**(6): 582–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
68. 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**(4): 1018–28.  
[PubMed Abstract](#) | [Publisher Full Text](#)
69. 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**(1): 45–56.  
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Aslam A, Singh J, 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**(4): 285–95.  
[PubMed Abstract](#) | [Publisher Full Text](#)
71. **F** 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**: 147–54.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
72. 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**(9): 976–82.  
[PubMed Abstract](#) | [Publisher Full Text](#)
73. Harris M, Eastman R, Cowie C: **Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population.** *Diabetes Care*. 1993; **16**(11): 1446–52.  
[PubMed Abstract](#) | [Publisher Full Text](#)
74. Smith AG, Singleton JR: **Impaired glucose tolerance and neuropathy.** *Neurologist*. 2008; **14**(1): 23–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
75. 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**(5): 578–85.  
[PubMed Abstract](#) | [Publisher Full Text](#)
76. Bennett M: **The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs.** *Pain*. 2001; **92**(1–2): 147–57.  
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Krause SJ, Backonja MM: **Development of a neuropathic pain questionnaire.** *Clin J Pain*. 2003; **19**(5): 306–14.  
[PubMed Abstract](#) | [Publisher Full Text](#)
78. Unal-Cevik I, Sarioglu-Ay S, Evcik D: **A comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: validity and reliability of the Turkish version of DN4.** *J Pain*. 2010; **11**(11): 1129–35.  
[PubMed Abstract](#) | [Publisher Full Text](#)
79. **F** Gibbons CH, Freeman R: **Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes.** *Brain*. 2015; **138**(Pt 1): 43–52.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
80. **F** 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**(8): 1446–55.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. 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**(11): 2263–73.  
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Marshall AG, Lee-Kubli C, Azmi S, *et al.*: **Spinal Disinhibition in Experimental and Clinical Painful Diabetic Neuropathy.** *Diabetes*. 2017; **66**(5): 1380–90.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Botney M, Fields HL: **Amitriptyline potentiates morphine analgesia by a direct action on the central nervous system.** *Ann Neurol*. 1983; **13**(2): 160–4.  
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Benbouzid M, Gavériaux-Ruff C, Yalcin I, *et al.*: **Delta-opioid receptors are critical for tricyclic antidepressant treatment of neuropathic allodynia.** *Biol Psychiatry*. 2008; **63**(6): 633–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
85. de Gandarias JM, Echevarria E, Acebes I, *et al.*: **Effects of imipramine administration on mu-opioid receptor immunostaining in the rat forebrain.** *Arzneimittelforschung*. 1998; **48**(7): 717–9.  
[PubMed Abstract](#)
86. **F** Moore RA, Derry S, Aldington D, *et al.*: **Amitriptyline for neuropathic pain in adults.** *Cochrane Database Syst Rev*. 2015; (7): CD008242.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
87. **F** Hossain SM, Hussain SM, Ekram AR: **Duloxetine in Painful Diabetic Neuropathy: A Systematic Review.** *Clin J Pain*. 2016; **32**(11): 1005–10.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
88. Lunn MP, Hughes RA, Wiffen PJ: **Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia.** *Cochrane Database Syst Rev*. 2014; (1): CD007115.  
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Lesser H, Sharma U, LaMoreaux L, *et al.*: **Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial.** *Neurology*. 2004; **63**(11): 2104–10.  
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Rosenstock J, Tuchman M, LaMoreaux L, *et al.*: **Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial.** *Pain*. 2004; **110**(3): 628–38.  
[PubMed Abstract](#) | [Publisher Full Text](#)
91. Arezzo JC, Rosenstock J, LaMoreaux L, *et al.*: **Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial.** *BMC Neurol*. 2008; **8**: 33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
92. Snedecor SJ, Sudharshan L, Cappelleri JC, *et al.*: **Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy.** *Pain Pract*. 2014; **14**(2): 167–84.  
[PubMed Abstract](#) | [Publisher Full Text](#)
93. Iqbal Z, Azmi S, Yadav R, *et al.*: **Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy.** *Clin Ther*. 2018; **40**(6): 828–49.  
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Javed S, Alam U, Malik RA: **Mirogabalin and emerging therapies for diabetic neuropathy.** *J Pain Res*. 2018; **11**: 1559–66.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
95. **F** Merante D, Rosenstock J, Sharma U, *et al.*: **Efficacy of Mirogabalin (DS-5565) on Patient-Reported Pain and Sleep Interference in Patients with Diabetic Neuropathic Pain: Secondary Outcomes of a Phase II Proof-of-Concept Study.** *Pain Med*. 2017; **18**(11): 2198–207.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
96. Vinik A, Rosenstock J, Sharma U, *et al.*: **Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: a randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study.** *Diabetes Care*. 2014; **37**(12): 3253–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)
97. **F** Duehmkne RM, Derry S, Wiffen PJ, *et al.*: **Tramadol for neuropathic pain in adults.** *Cochrane Database Syst Rev*. 2017; (6): CD003726.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
98. Vinik AI, Shapiro DY, Rauschkolb C, *et al.*: **A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended**

release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care*. 2014; 37(8): 2302–9. [PubMed Abstract](#) | [Publisher Full Text](#)

99. **F** Niesters M, Proto PL, Aarts L, et al.: Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth*. 2014; 113(1): 148–56. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

100. Schwartz S, Etropolski 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 Investig*. 2015; 35(2): 95–108. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

101. 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. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

102. **F** 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(12): 2616–25. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

103. 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(10): 2171–9. [PubMed Abstract](#) | [Publisher Full Text](#)

104. **F** Boyle J, Eriksson ME, 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(12): 2451–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

105. Yuen KC, Baker NR, Rayman G: Treatment of Chronic Painful Diabetic Neuropathy With Isosorbide Dinitrate Spray: a double-blind placebo-controlled cross-over study. *Diabetes Care*. 2002; 25(10): 1699–703. [PubMed Abstract](#) | [Publisher Full Text](#)

106. Rayman G, Baker NR, Krishnan ST: Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care*. 2003; 26(9): 2697–8. [PubMed Abstract](#) | [Publisher Full Text](#)

107. Agrawal RP, Choudhary R, Sharma P, et al.: Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract*. 2007; 77(2): 161–7. [PubMed Abstract](#) | [Publisher Full Text](#)

108. Agrawal RP, Goswami J, Jain S, et al.: Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. *Diabetes Res Clin Pract*. 2009; 83(3): 371–8. [PubMed Abstract](#) | [Publisher Full Text](#)

109. Alam U, Jeziorska M, Petropoulos IN, et al.: Diagnostic utility of corneal confocal microscopy and intra-epidermal nerve fibre density in diabetic neuropathy. *PLoS One*. 2017; 12(7): e0180175. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

110. Kalteniece A, Ferdousi M, Petropoulos I, et al.: Greater corneal nerve loss at the inferior whorl is related to the presence of diabetic neuropathy and painful diabetic neuropathy. *Sci Rep*. 2018; 8(1): 3283. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

111. **F** Eijkenboom I, Sopacua M, Hoeijmakers JGJ, et al.: Yield of peripheral sodium channels gene screening in pure small fibre neuropathy. *J Neurol Neurosurg Psychiatr*. 2018; pii: jnnp-2018-319042. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

112. Huang J, Han C, Estacion M, et al.: Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. *Brain*. 2014; 137(Pt 6): 1627–42. [PubMed Abstract](#) | [Publisher Full Text](#)

113. Lauria G, Ziegler D, Malik R, et al.: The role of sodium channels in painful diabetic and idiopathic neuropathy. *Curr Diab Rep*. 2014; 14(10): 538. [PubMed Abstract](#) | [Publisher Full Text](#)

114. Spallone V, Ziegler D, Freeman R, et al.: Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev*. 2011; 27(7): 639–53. [PubMed Abstract](#) | [Publisher Full Text](#)

115. Ziegler D, Voss A, Rathmann W, et al.: Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: the KORA S4 survey. *Diabetologia*. 2015; 58(5): 1118–28. [PubMed Abstract](#) | [Publisher Full Text](#)

116. Carnethon MR, Prineas RJ, Temprosa M, et al.: The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care*. 2006; 29(4): 914–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

117. Vinik AI, Maser RE, Mitchell BD, et al.: Diabetic Autonomic Neuropathy. *Diabetes Care*. 2003; 26(5): 1553–79. [PubMed Abstract](#) | [Publisher Full Text](#)

118. 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(1): 31–8. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

119. Pop-Busui R, Low PA, Waberski BH, et al.: Effects of Prior Intensive Insulin Therapy on Cardiac Autonomic Nervous System Function in Type 1 Diabetes Mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation*. 2009; 119(22): 2886–93. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

120. Low PA, Benrud-Larson LM, Sletten DM, et al.: Autonomic symptoms and diabetic neuropathy: a population-based study. *Diabetes Care*. 2004; 27(12): 2942–7. [PubMed Abstract](#) | [Publisher Full Text](#)

121. 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(7): 1360–6. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

122. **F** 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(7): 1578–84. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

123. Maser RE, Mitchell BD, Vinik AI, et al.: The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*. 2003; 26(6): 1895–901. [PubMed Abstract](#) | [Publisher Full Text](#)

124. Vinik AI, Ziegler D: Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007; 115(3): 387–97. [PubMed Abstract](#) | [Publisher Full Text](#)

125. Dinh W, Füh R, Lankisch M, et al.: Cardiovascular autonomic neuropathy contributes to left ventricular diastolic dysfunction in subjects with Type 2 diabetes and impaired glucose tolerance undergoing coronary angiography. *Diabet Med*. 2011; 28(3): 311–8. [PubMed Abstract](#) | [Publisher Full Text](#)

126. Astrup AS, Tarnow L, Rossing P, et al.: Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care*. 2006; 29(2): 334–9. [PubMed Abstract](#) | [Publisher Full Text](#)

127. Ziegler D, Keller J, Maier C, et al.: Diabetic neuropathy. *Exp Clin Endocrinol Diabetes*. 2014; 122(7): 406–15. [PubMed Abstract](#) | [Publisher Full Text](#)

128. Mellegers MA, Furlan AD, Mailis A: Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature. *Clin J Pain*. 2001; 17(4): 284–95. [PubMed Abstract](#) | [Publisher Full Text](#)

129. Rudroju N, Bansal D, Talakkokkula ST, et al.: Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. *Pain Physician*. 2013; 16(6): E705–14. [PubMed Abstract](#)

130. Tanenberg RJ, Irving GA, Risser RC, et al.: Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc*. 2011; 86(7): 615–26. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

131. Goldstein DJ, Lu Y, Detke MJ, et al.: Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005; 116(1–2): 109–18. [PubMed Abstract](#) | [Publisher Full Text](#)

132. Wasan AD, Ossanna MJ, Raskin J, et al.: Safety and efficacy of duloxetine in the treatment of diabetic peripheral neuropathic pain in older patients. *Curr Drug Saf*. 2009; 4(1): 22–9. [PubMed Abstract](#) | [Publisher Full Text](#)

133. **F** Trouvin AP, Perrot S, Lloret-Linares C: Efficacy of Venlafaxine in Neuropathic Pain: A Narrative Review of Optimized Treatment. *Clin Ther*. 2017; 39(6): 1104–22. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

134. Rowbotham MC, Goli V, Kunz NR, et al.: Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain*. 2004; 110(3): 697–706. [PubMed Abstract](#) | [Publisher Full Text](#)

135. Markovits E, Gilhar A: Capsaicin—an effective topical treatment in pain. *Int J Dermatol*. 1997; 36(6): 401–4. [PubMed Abstract](#) | [Publisher Full Text](#)

136. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group. *Arch Intern Med*. 1991; 151(11): 2225–9. [PubMed Abstract](#) | [Publisher Full Text](#)

137. Polydefkis M, Hauer P, Sheth S, et al.: The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. *Brain*. 2004; 127(Pt 7): 1606–15. [PubMed Abstract](#) | [Publisher Full Text](#)

138. **F** Burness CB, McCormack PL: Capsaicin 8 % Patch: A Review in Peripheral Neuropathic Pain. *Drugs*. 2016; 76(1): 123–34. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

139. Wolff RF, Bala MM, Westwood M, et al.: 5% lidocaine medicated plaster in painful diabetic peripheral neuropathy (DPN): a systematic review. *Swiss Med*

Wkly. 2010; **140**(21–22): 297–306.  
[PubMed Abstract](#)

140. Suarez GA, Opfer-Gehrking TL, Offord KP, *et al.*: **The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms.** *Neurology*. 1999; **52**(3): 523–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)

141. Freeman R: **Autonomic peripheral neuropathy.** *Lancet*. 2005; **365**(9466): 1259–70.  
[PubMed Abstract](#) | [Publisher Full Text](#)

142. Boulton AJM, Vinik AI, Arezzo JC, *et al.*: **Diabetic neuropathies: a statement by the American Diabetes Association.** *Diabetes Care*. 2005; **28**(4): 956–62.  
[PubMed Abstract](#) | [Publisher Full Text](#)

143. Valensi P, Pariès J, Attali JR, *et al.*: **Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications—the French multicenter study.** *Metabolism*. 2003; **52**(7): 815–20.  
[PubMed Abstract](#) | [Publisher Full Text](#)

144. Witte DR, Tesfaye S, Chaturvedi N, *et al.*: **Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus.** *Diabetologia*. 2005; **48**(1): 164–71.  
[PubMed Abstract](#) | [Publisher Full Text](#)

145. 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**(1): 101–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)

146. 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**(10): 2244–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

147. 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**(3): 369–73.  
[PubMed Abstract](#) | [Publisher Full Text](#)

148. 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**(8): 1835–44.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

149. Pop-Busui R: **Cardiac autonomic neuropathy in diabetes: a clinical perspective.** *Diabetes Care*. 2010; **33**(2): 434–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

150. Freeman R, Abuzinadah AR, Gibbons C, *et al.*: **Orthostatic Hypotension: JACC State-of-the-Art Review.** *J Am Coll Cardiol*. 2018; **72**(11): 1294–309.  
[PubMed Abstract](#) | [Publisher Full Text](#)

151. 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**(8): 1567–82.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

152. Freeman R: **Clinical practice. Neurogenic orthostatic hypotension.** *N Engl J Med*. 2008; **358**(6): 615–24.  
[PubMed Abstract](#) | [Publisher Full Text](#)

153. Kaufmann H: **Droxidopa for symptomatic neurogenic orthostatic hypotension: what can we learn?** *Clin Auton Res*. 2017; **27**(Suppl 1): 1–3.  
[PubMed Abstract](#) | [Publisher Full Text](#)

154. Parkman HP, Hasler WL, Fisher RS: **American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis.** *Gastroenterology*. 2004; **127**(5): 1592–622.  
[PubMed Abstract](#) | [Publisher Full Text](#)

155. Kumar M, Chapman A, Javed S, *et al.*: **The Investigation and Treatment of Diabetic Gastroparesis.** *Clin Ther*. 2018; **40**(6): 850–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)

156. Muroa S, Hosokawa H: **Serotonin 5-HT3 receptor antagonist for treatment of severe diabetic diarrhea.** *Diabetes Care*. 2010; **33**(3): e38.  
[PubMed Abstract](#) | [Publisher Full Text](#)

157. Ogbonnaya KI, Arem R: **Diabetic diarrhea. Pathophysiology, diagnosis, and management.** *Arch Intern Med*. 1990; **150**(2): 262–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)

158. Feldman HA, Goldstein I, Hatzichristou DG, *et al.*: **Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study.** *J Urol*. 1994; **151**(1): 54–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)

159. Azmi S, Ferdousi M, Alam U, *et al.*: **Small-fibre neuropathy in men with type 1 diabetes and erectile dysfunction: a cross-sectional study.** *Diabetologia*. 2017; **60**(6): 1094–101.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

160. Giugliano F, Maiorino M, Bellastella G, *et al.*: **Determinants of erectile dysfunction in type 2 diabetes.** *Int J Impot Res*. 2010; **22**(3): 204–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)

161. van den Eeden SK, Sarma AV, Rutledge BN, *et al.*: **Effect of intensive glycemic control and diabetes complications on lower urinary tract symptoms in men with type 1 diabetes: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.** *Diabetes Care*. 2009; **32**(4): 664–70.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

162. Enzlin P, Mathieu C, van den Bruel A, *et al.*: **Sexual dysfunction in women with type 1 diabetes: a controlled study.** *Diabetes Care*. 2002; **25**(4): 672–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)

163. **F** Hackett G, Kirby M, Wylie K, *et al.*: **British Society for Sexual Medicine Guidelines on the Management of Erectile Dysfunction in Men-2017.** *J Sex Med*. 2018; **15**(4): 430–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

164. **F** Mulhall JP, Giraldi A, Hackett G, *et al.*: **The 2018 Revision to the Process of Care Model for Evaluation of Erectile Dysfunction.** *J Sex Med*. 2018; **15**(9): 1280–92.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

165. **F** Mulhall JP, Giraldi A, Hackett G, *et al.*: **The 2018 Revision to the Process of Care Model for Management of Erectile Dysfunction.** *J Sex Med*. 2018; **15**(10): 1434–45.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

166. **F** Mulhall JP, Carlsson M, Stecher V, *et al.*: **Predictors of Erectile Function Normalization in Men With Erectile Dysfunction Treated With Placebo.** *J Sex Med*. 2018; **15**(6): 866–72.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

167. Gruenewald I, Kitrey ND, Appel B, *et al.*: **Low-Intensity Extracorporeal Shock Wave Therapy in Vascular Disease and Erectile Dysfunction: Theory and Outcomes.** *Sex Med Rev*. 2013; **1**(2): 83–90.  
[PubMed Abstract](#) | [Publisher Full Text](#)

168. **F** Kitrey ND, Vardi Y, Appel B, *et al.*: **Low Intensity Shock Wave Treatment for Erectile Dysfunction-How Long Does the Effect Last?** *J Urol*. 2018; **200**(1): 167–70.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

169. **F** Bechara A, Casabé A, De Bonis W, *et al.*: **Twelve-Month Efficacy and Safety of Low-Intensity Shockwave Therapy for Erectile Dysfunction in Patients Who Do Not Respond to Phosphodiesterase Type 5 Inhibitors.** *Sex Med*. 2016; **4**(4): e225–e232.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

170. **F** Elhanbly SM, Abdel-Gawad MM, Elkholly AA, *et al.*: **Nocturnal penile erections: A retrospective study of the role of RigiScan in predicting the response to sildenafil in erectile dysfunction patients.** *J Adv Res*. 2018; **14**: 93–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

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