Can J Diabetes 42 (2018) S217–S221

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Neuropathy

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Elevated blood glucose levels, elevated triglycerides, high body mass index, smoking and hypertension are risk factors for neuropathy.
- Intensive glycemic control is effective for the primary prevention or secondary intervention of neuropathy in people with type 1 diabetes.
- In people with type 2 diabetes, lower blood glucose levels are associated with a reduced frequency of neuropathy.
- Simple physical examination screening tests, such as the 10 g monofilament (on the dorsal aspect of the great toe bilaterally) and vibration perception (with 128 Hz tuning fork), perform reasonably well for the identification of neuropathy and prediction of its future onset.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Exposure to high blood glucose levels over an extended period of time can cause diabetic peripheral neuropathy or damage to the nerves that go to the feet, legs and, when markedly advanced, to the hands and arms.
- The most common symptoms of diabetic peripheral neuropathy are loss of sensations in the toes and feet, and presence of symptoms, such as sharp shooting pains, burning, tingling, a feeling of being pricked with pins, throbbing and numbness.
- Diabetic peripheral neuropathy increases the risk for foot ulcers and amputation.
- Your health-care provider or foot care specialist can test for diabetic peripheral neuropathy by lightly pressing a thin nylon rod (10 g monofilament) and by using the 128 Hz tuning fork on the top surface of your big toe.
- Although there is no cure, there are many ways you can effectively manage diabetic peripheral neuropathy, including:
  - Proper foot care, including daily foot inspection
  - Effective blood glucose control
  - Medications that may help with nerve pain
- Diabetic autonomic neuropathies affect the part of the nervous system responsible for control of internal body functions and may target the heart (cardiac autonomic neuropathy), gastrointestinal tract, and genitourinary system, and can cause sexual dysfunction.

Introduction

Diabetes is the leading cause of neuropathy in North America (1). Estimates of the prevalence vary depending on the diagnostic criteria and population studied. A reasonable figure based on several large studies is that detectable sensorimotor polyneuropathy (diffuse and symmetric neuropathy) will develop within 10 years of the onset of diabetes in 40% to 50% of people with type 1 (1–3) and type 2 diabetes (4–6). While clinical neuropathy is uncommon in people with type 1 diabetes within the first 5 years after the onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis or even in the prediabetes stage (4–7). Risk factors for neuropathy include elevated blood glucose (BG) levels, elevated triglycerides (TG), high body mass index (BMI), smoking and hypertension (8). There appear to be multifactorial mechanisms behind the pathogenesis of diabetic neuropathy (9) and it may represent a unique form of neurodegeneration (9,10).

The most common form of diabetic neuropathy is distal symmetric polyneuropathy (DSPN). Symptoms vary according to the class of sensory fibres involved. The most common early symptoms are from small fibre involvement and include pain (e.g. sharp, shooting) and dysesthesias (e.g. burning). Pain may be present in the presence of a normal clinical examination and normal nerve conduction studies, which are a measure of large fibre function (11). The involvement of large fibres may cause numbness, tingling and loss of protective sensation.

Neuropathic pain is frequently bothersome and often limits physical activity, quality of life and work productivity (3,11–13). Additionally, people with neuropathy utilize more health resources than those without (14). Foot ulceration, which depends on the degree of foot insensitivity (15), and amputation are important and costly sequelae of diabetic neuropathy (16).

Diabetic autonomic neuropathies (DAN) affect the autonomic neurons and may target the innervation of the heart (cardiac autonomic neuropathy [CAN]), gastrointestinal tract, genitourinary system, sexual function, pupillary responses and sweating. Specialized laboratories that study clinical autonomic disorders, including DAN, are available at some centres (17).

The prevalence of CAN increases with diabetes duration in people with type 1 and type 2 diabetes. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study, prevalence rates of at least 30% were observed after 20 years of type 1 diabetes (2,18). CAN may be present in up to 60% of people with type 2 diabetes after 15 years (19). CAN may be identified by heart rate variability and has been shown to be a risk factor for mortality in diabetes (20–22); however, further study is required to determine if interventions are helpful in reducing the risk of subsequent cardiac events and mortality.

Other features of CAN are postural hypotension, and resting tachycardia (i.e. 100 beats/min). For postural hypotension, the diagnosis is made by measuring supine, followed by a 1-minute standing blood pressure (BP) and pulse. A fall of greater than 20 mmHg systolic

Conflict of interest statements can be found on page S219.

https://doi.org/10.1016/j.jcjd.2017.10.028

without an appropriate increase in heart rate is significant. Treatment includes conservative measures to increase fluid and salt intake, caution with exacerbating medications, compression stockings and sleeping with the head of the bed elevated. Specific therapies include fludrocortisone, midodrine and droxidopa (approved in the United States but not Canada), with care taken to monitor for supine hypertension (10,23,24).

Gastrointestinal neuropathies may be associated with gastroparesis, constipation, diarrhea (especially nocturnal), and incontinence. A gastric emptying study may be helpful in diagnosis. Treatment approaches include dietary measures, withdrawal of exacerbating medications (e.g. glucagon-like peptide-1 [GLP-1] receptor agonists, opioids) and, in severe instances, temporary use of the prokinetic agent, metoclopramide, but its use is limited by risk of extrapyramidal side effects.

Bladder dysfunction in DAN includes loss of bladder sensation and later detrusor dysfunction with overflow incontinence, predisposition to infection and inability to empty. Bladder function should be evaluated in people with diabetes with recurrent urinary tract infections, pyelonephritis or incontinence. The use of amitriptyline is contraindicated in people with diabetic bladder involvement owing to potential anticholinergic side effects.

Erectile dysfunction in men is the most common symptom of DAN with a prevalence of up to 40% (25), although it may be associated with the presence or the absence of DSPN. Treatment includes phosphodiesterase-5 inhibitors for mild erectile dysfunction, local prostaglandin injections, vacuum devices or prostheses (see Sexual Dysfunction and Hypogonadism in Men with Diabetes chapter, p. S228).

Sudomotor abnormalities are loss of sweating in the extremities with inappropriate truncal sweating, dry skin or heat intolerance. Gustatory sweating may occur and consists of excessive sweating in the head and neck triggered by food consumption or the smell of food.

Mononeuropathies, or focal neuropathies, can occur with involvement of the median, ulnar, radial and common peroneal nerves. Carpal tunnel syndrome and ulnar neuropathy at the elbow is also common in diabetes and can be distinguished from polyneuropathy by electrophysiological studies (26).

There are other forms of diabetic-related neuropathy that are less common, such as diabetic radiculoplexus neuropathy (also known as diabetic amyotrophy or diabetic polyradiculoneuropathy), cranial neuropathies (primarily involving cranial nerves III, IV, VI, and VII), thoracic radiculopathy and others (27). Diabetes may also target other parts of the nervous system, including the brain (28).

The underdiagnosis of neuropathy is a fundamental problem in the primary care of people with diabetes and impedes the benefits of early identification, the management necessary to achieve improved glycemic control and the prevention of neuropathy-related sequelae (29). However, it is important to exclude other causes of neuropathy besides diabetes by way of obtaining a family and medication (including alcohol) history. Relevant investigations may include: serum B12 (particularly with use of metformin), folic acid, thyroid function, complete blood count, serum creatinine and protein electrophoresis.

Screening for Peripheral Neuropathy

Asymptomatic screening for neuropathy can be performed rapidly and reliably using the 10 g Semmes-Weinstein monofilament or the 128 Hz tuning fork over the dorsal aspect of the great toe bilaterally (30–34). Other screening tests can include pinprick or temperature (starting distally bilaterally and moving proximally until a sensory threshold is identified) and ankle reflexes. Methods for using the monofilament or tuning fork to detect diabetic neuropathy are outlined in Appendix 11A. Rapid Screening for Diabetic Neuropathy Using the 10 g Semmes-Weinstein Monofilament, and Appendix 11B. Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork (30,31,34). Additionally, several clinical scoring systems based on composite measures of symptoms and signs have been developed and evaluated for identification of neuropathy, but it is not clear if these more complex procedures have benefit over simplified screening tests for neuropathy identification. Evaluation for neuropathy in the lower limbs should also accompany the evaluation of vascular supply and skin integrity as outlined in the Foot Care chapter, p. S222. In addition, it is important to recognize that the 10 g monofilament test for annual DSPN screening is different than the testing used to identify a foot at high risk for ulceration in the context of recognized neuropathy. Testing to assess risk for foot ulceration generally requires testing of 3 sites on each foot (see Appendix 12: Monofilament Testing in the Diabetic Foot, p. S322).

Individuals with asymmetrical manifestations of neuropathy, greater motor than sensory impairments, or rapidly progressive symptoms or signs of neuropathy may have nondiabetic causes of neuropathy that may require more careful evaluation, and referral for additional neurological evaluation should be considered.

Management of Diabetic Neuropathy

Intensive glycemic control is effective for the primary prevention and secondary intervention of neuropathy in people with type 1 diabetes (3,6,35,36). In fact, the benefits of intensive insulin treatment persist for over a decade for the primary prevention of neuropathy (37). In those with type 2 diabetes, target BG levels are associated with a reduced frequency of neuropathy (5,12,38). No other clearly efficacious disease-modifying treatments are currently available. Multiple treatments are available for the management of neuropathic pain, and detailed evidence-based guidelines on the treatment of painful diabetic neuropathy (PDN) have been published (39). An important observation is that few people have complete relief of painful symptoms with any treatment, and that a 30% to 50% reduction in baseline pain, usually measured by a visual analogue scale of 0 to 10 out of 10 maximal pain intensity, is considered to be a clinically meaningful response.

There are insufficient comparative studies to recommend which oral medication should be used first line, although the primary use of opioids for PDN, despite clinical trial evidence for pain efficacy (40–44), is not recommended due to the potential for dependency, tolerance, dose escalation and diversion (39,45). Anticonvulsants (46–54) and antidepressants (55–64) are most commonly used as first-line therapy. Details are listed in Table 1. Pregabalin and duloxetine have received approval for the treatment of neuropathic pain in diabetes by Health Canada.

Other effective therapeutic options include topical nitrate sprays (65,66), topical capsaicin (67–70) and transcutaneous electrical nerve stimulation (71,72). However, effective treatment with capsaicin involves short-term pain that limits its acceptability and generalizability in clinical practice. The surgical release of distal lower limb nerves is not recommended due to lack of evidence supporting efficacy (73) and the possible complications of foot and ankle surgery in people with diabetes.

Dose ranges for painful neuropathic symptoms described in Table 1 are for adults and are taken from published trials; smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and hepatic dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

Table 1
Treatment options for the management of painful diabetic peripheral neuropathy

	Suggested starting dose	Suggested titration if tolerated	Suggested maximal tolerated dose	Estimated monthly cost for starting dose
Anticonvulsants				
Gabapentin† (46,74)	300 mg BID or qhs	May titrate slowly up to 600 mg po qid	3,600 mg/day	BID: $24.34 (60) QD: $18.32 (30)
Pregabalin (47–49,52,53,75)	75 mg BID	May titrate slowly up to 300 mg po bid	600 mg/day	$98.77 (60)
Valproate (50,51)	250 mg BID	May titrate slowly up to 500 mg po bid	1,500 mg/day	$12.37 (60)
Antidepressants				
Amitriptyline †(56,57,61,72)	10 mg QHS	May titrate slowly up to 100 mg po qhs	150 mg/day	$14.49 (30)
Duloxetine (60,64)	30 mg OD	May titrate to 60 mg po od	120 mg/day	$28.22 (30)
Venlafaxine† (62,63,75–79)	37.5 mg BID	May titrate slowly up to 150 mg po bid	300 mg/day	$23.16 (60)
Opioids*				
***Note:* Although the following agents have demonstrated efficacy for neuropathic pain, their use should be selective, after other options have failed to be effective, and clinicians must be aware of the risks of tolerance, abuse, dependency and addiction (45). The limited use of these agents should follow the principles of the *2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain* (54).**				
Tramadol (44)*	50 mg QID	May titrate slowly up to 50 mg po qid	400 mg/day	$100.45 (120)
Tapentadol ER (40)*	100 mg BID	May titrate slowly up to 250 mg po bid	250 mg po bid	$118.49 (60)
Dextromethorphan (42)*	100 mg QID	May titrate slowly up to 200 mg po qid	960 mg/day	requires compounding of the capsules
Morphine sustained release (74)*	15 mg BID	May titrate slowly up to 60 mg po bid	180 mg/day	$27.61 (60)
Oxycodone ER (43)*	10 mg BID	May titrate slowly up to 40 mg po bid	160 mg/day	$42.60 (60)
Others				
Topical nitrate sprays (65,66,70)	30 mg spray to legs QHS	May titrate slowly up to 30 mg spray to legs bid	60 mg/day	
Capsaicin cream (68,69)**	0.075% cream applied 3–4 times per day	May titrate to 5–6 times per day	5–6 applications per day	$17.99
Transcutaneous electrical nerve stimulation	-	-	-	-

BID, 2 times a day; *OD*, once daily; *QHS*, every bedtime; *QID*, 4 times a day.
Dose ranges are for adults and are taken from published trials—smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and liver dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.
* Use with caution due to risks of dependency and tolerance; not advised as first-line therapy, and generally considered a treatment of last resort for painful neuropathy.
† Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated with diabetic peripheral neuropathy.

RECOMMENDATIONS

1. In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter [Grade D, Consensus]. In people with type 1 diabetes, annual screening should commence after 5 years' post-pubertal duration of diabetes [Grade D, Consensus].

2. Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10 g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Grade A, Level 1 (31,34)] (see Appendices 11A and 11B. Rapid Screening for Diabetic Neuropathy).

3. People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy [Grade A, Level 1A (3,35) for type 1 diabetes; Grade B, Level 2 (38) for type 2 diabetes].

4. The following agents may be used alone or in combination for relief of painful peripheral neuropathy:
   a. Anticonvulsants (pregabalin [Grade A, Level 1 (47,52)], gabapentin† [Grade B, Level 2 (46,74)], valproate† [Grade B, Level 2 (50,51)]
   b. Antidepressants (amitriptyline†, duloxetine, venlafaxine†) [Grade B, Level 2 (56,57,60,61,63,75)]
   c. Topical nitrate spray† [Grade B, Level 2 (65,66,70)]
   d. In people not responsive to the above agents, opioid analgesics (tramadol, tapentadol ER, oxycodone ER) may be used [Grade B, Level 2 (41,43,44)]. Prescribers should be cautious due to risks of abuse, dependency and tolerance, and follow the recommendations of the *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain* (54) [Grade D, Consensus].

Footnote:
†Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated specifically with diabetic peripheral neuropathy.
Most studies failed to achieve Grade A, Level 1 due to a <80% completion rate (39).

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *BMI*, body mass index; *CAD*, cardiac autonomic neuropathy; *DAN*, diabetic autonomic neuropathy; *DPN*, diabetic peripheral neuropathy; *PDN*, painful diabetic neuropathy.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Foot Care, p. S222
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

Relevant Appendices

Appendix 11A. Rapid Screening for Diabetic Neuropathy Using the 10 g Semmes-Weinstein Monofilament
Appendix 11B. Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork
Appendix 12. Monofilament Testing in the Diabetic Foot

Author Disclosures

Dr. Bril reports grants from Pfizer and Lilly, during the conduct of the study; and other support from Pfizer, outside the submitted work. Dr. Breiner reports grants from GBS-CIDP Foundation International, Grifols, Inc, and other support from Pfizer, outside the submitted work. No other authors have anything to disclose.

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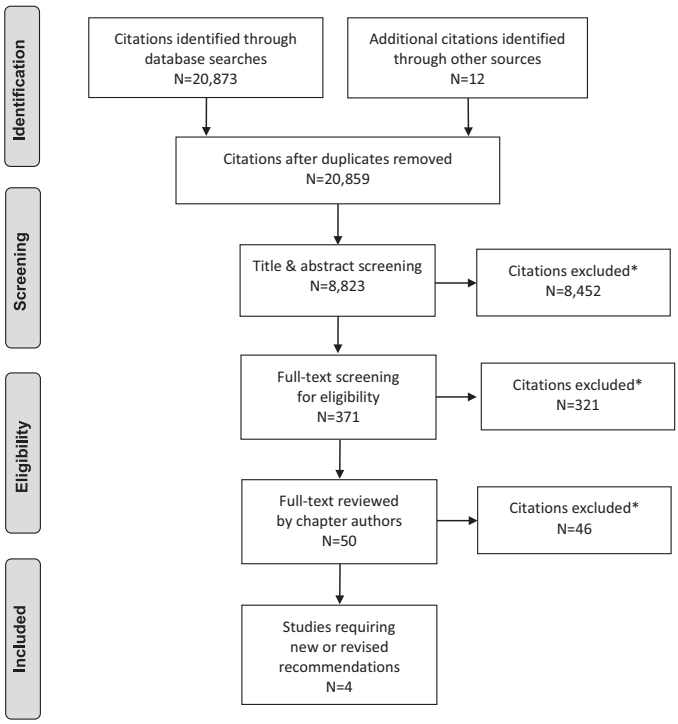
Literature Review Flow Diagram for Chapter 31: Neuropathy



*Excluded based on: population, intervention/exposure, comparator/control or study design

From reference 80.

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