Diabetes-related sensory peripheral neuropathy

Epidemiology

- Neuropathy is the most common and costly complication of diabetes.
- Diabetic sensorimotor polyneuropathy (DSPN) is the most common form, affecting 33% of people with diabetes.
- Up to 50% of people with DSPN are asymptomatic.
- 8–10% of cases may be present at diagnosis. Can occur in pre-diabetes.
- Significantly unrecognised, unreported and untreated.
- Cannot be reversed: prevention is only option.

Risk factors

- Duration of diabetes.
- Poor glycaemic control, glycaemic variability.
- Older age.
- Type 2 diabetes (more common than in type 1).
- Smoking.
- Obesity.
- Metabolic syndrome.

Pathophysiology

Possible mechanisms include elevated blood glucose over time causing damage to the small blood vessels (microvascular disease). Narrowing of the vessels supplying the myelin sheath leads to ischaemia and causes damage to the nerve cells and loss of normal function. High blood glucose also causes high-energy products (free radicals), which also damage nerve cells. Other mechanisms postulated.

Perpetuating factors

Neuropathic pain leads to functional impairment such as sleep disturbance (90% of patients) and anxiety and depression (45%), leading to lack of energy, memory difficulties, poor concentration and mood swings. Increased CVD and mortality risk.

Main types of diabetes-related neuropathy

- Diabetic sensorimotor polyneuropathy (DSPN) is the most common.
  - Damage to large nerve fibres causes loss of vibration, touch and position sense and ankle jerks.
  - Damage to small nerve fibres leads to loss of protective sensation (**LOPS**) and loss of temperature discrimination.
  - Involvement of large and small fibres usually co-exists.
- Autonomic neuropathy, polyradiculopathies, diabetic amyotrophy and mononeuropathies will not be discussed here.

DSPN

- Defined clinically as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.
- Usually mild insidious onset with a predominance of sensory symptoms beginning distally in the toes and moving proximally into feet and calves; may involve hands in advanced cases.
- LOPS is an important cause of foot ulceration; also a prerequisite in the development of Charcot neuroarthropathy.
- LOPS and motor involvement contribute to falls and fractures.

Differential diagnosis (see Ziegler et al, 2022)

Consider causes other than DSPN if:

- Asymmetry
- More motor than sensory
- Rapid development or ongoing deterioration despite optimal glycaemic control
- Onset upper before lower limbs

Potential causes:

Metabolic disease
- Hyper- and hypothyroidism
- Renal disease (CKD stage 4 and 5)

Systemic disease
- Systemic vasculitis
- Paraproteinaemia, including monoclonal gammopathy
- Cancers and chemotherapy

Infectious disease
- HIV
- Hepatitis B
- Lyme disease

Nutritional
- B12 deficiency
- Post-gastroplasty
- Thiamine deficiency

Drugs
- Alcohol (common)
- Amiodarone
- Colchicine
- Vinca alkaloids (common)
- Platinum (common)
- Paclitaxel (common)

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Screening and diagnosis

- Due to a lack of licensed treatments that target the underlying nerve damage, prevention is key.
- All people with diabetes should be assessed for DSPN regularly (see ADA position statement; Pop-Busui et al, 2017):
  - **Type 2 diabetes:** At diagnosis and at least annually thereafter.
  - **Type 1 diabetes:** Five years after diagnosis and at least annually thereafter.
- All should receive an annual foot examination, including evaluation of neurological status, vascular status, foot structure and skin integrity (NICE, 2015).

Prompts when taking a history

- Important to realise many patients do not report symptoms to healthcare professionals as they can be unaware that there is a problem. **Always ask.**
- Patients rarely volunteer focal symptoms but often say they fall/trip or cannot climb stairs with ease. They often report that they feel they are walking on cotton wool.
- Therefore, important to enquire about positive and negative symptoms and any alteration in shape or function of the feet.

Signs and symptoms

- Neuropathic pain: present in up to 25% of individuals with DSPN. May be the first symptom that prompts seeking medical care.
  - Characteristically, pain is burning, lancinating, tingling or shooting (electric shock-like) in sensation.
  - Exaggerated response to painful stimuli (hyperalgesia); pain evoked by contact with e.g. socks, shoes and bedclothes (allodynia); unpleasant abnormal sensation (dysaesthesia); increased sensitivity to touch (hyperaesthesia).
- Involvement of the large nerve fibres may cause numbness, tingling without pain and loss of protective sensation (LOPS). **Despite LOPS, patients can still feel neuropathic pain**.
- Patients can also initially present with an insensate, numb foot due to the loss of the large nerve fibers.

Examination

- Careful history, signs/symptoms.
- Either temperature or pinprick sensation (to test small-fibre function).
- Vibration sensation using a 128 Hz tuning fork (to test large-fibre function).
- All patients should have an annual 10 g monofilament test to assess large fibre function (dorsum great toe) and risk of ulceration and amputation (sole of foot for LOPS).
  See How to guide (Diggle, 2021).
- Leg, knee, ankle and foot reflexes.

Management

- Optimise glucose control to prevent or slow the progression of DSPN. Optimise glucose control as early as possible to help prevent or delay development of DSPN. However, rapid tightening of glycaemic control may itself worsen neuropathy.
- Enhanced glucose control is much more effective at preventing neuropathy in type 1 diabetes than in type 2.

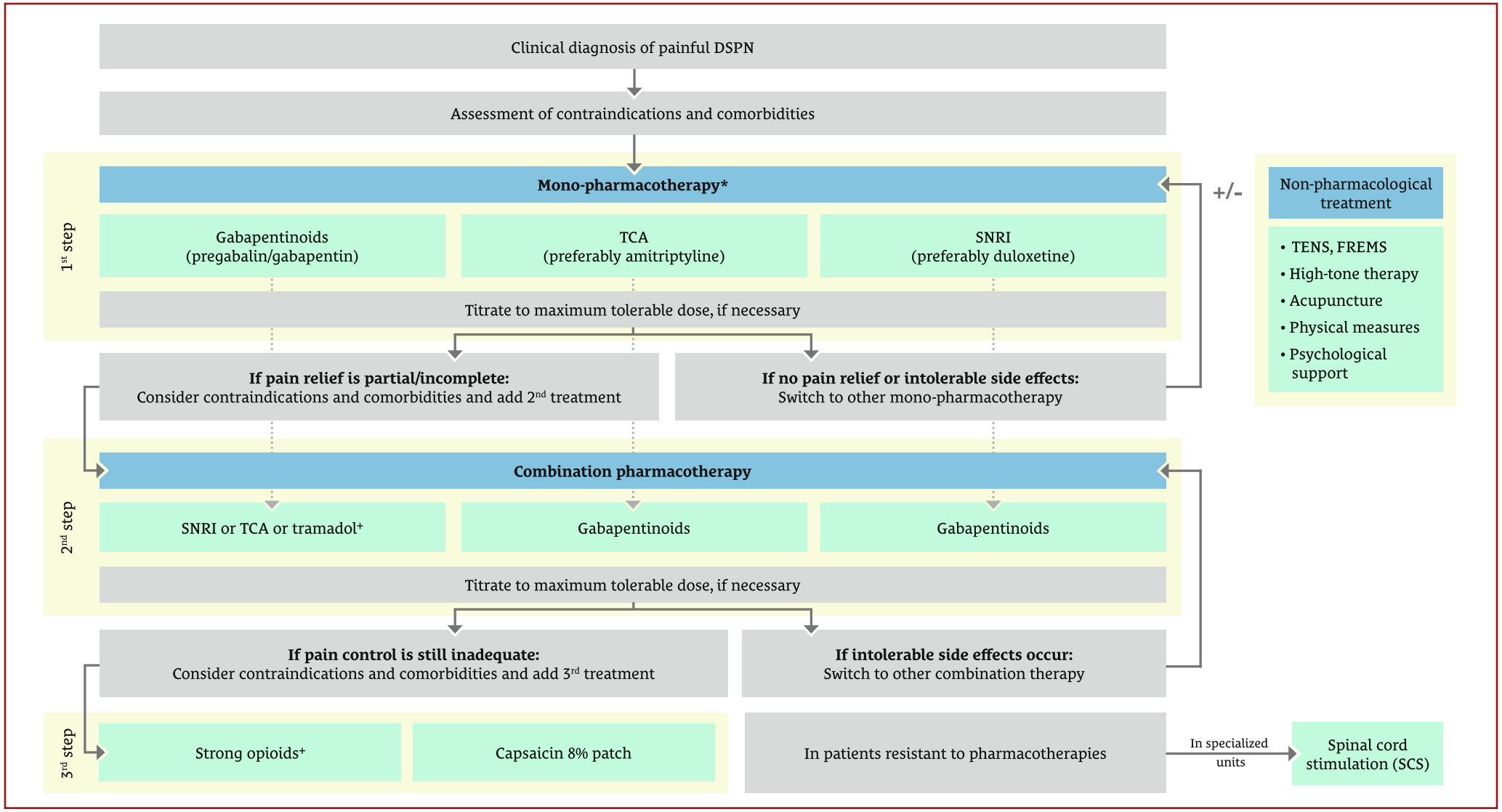
Holistic management for both prevention and treatment

- Manage cardiovascular risk factors.
- Healthy diet.
- 150 minutes of exercise per week (clinical guidance on safe exercise should be provided: if loss of protective sensation or any active foot lesion, weight-bearing exercise should be on the recommendation of the foot care team only).
- Stop smoking.
- Reduce/stop alcohol.
- Control blood pressure, glucose and lipids by using individualised patient targets.
- Offer CBT for associated depression and mental health issues.
- Advise patients to switch light on when getting up at night (to avoid trauma).
- Wear well-fitting slippers in the house.
- Avoid sandals outside.
- Always check shoes for stones, etc.
- Check water temperature with hand or bath thermometer.

Painful diabetic neuropathy

- The main treatments: management of the underlying diabetes and drugs for the relief of pain.
- Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment (see ***Figure 1*** and ***Box A***).
- Consider tramadol only if acute rescue therapy is needed. Avoid opiates in chronic situation.
- Consider capsaicin cream for people with localised neuropathic pain who wish to avoid or cannot tolerate oral treatment.

Figure 1. Analgesic pharmacotherapy and non-pharmacological treatment options in painful DSPN in clinical practice.



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*Pathogenetically oriented treatment approaches may also be considered; +for short-term use only, whenever possible.

DSPN=diabetic sensorimotor polyneuropathy; TCA=tricyclic antidepressants; SNRI=serotonin–norepinephrine reuptake inhibitors; TENS=transcutaneous electrical nerve stimulation; FREMS=frequency-modulated electromagnetic neural stimulation.

Box A. Prescribing advice: Medications for diabetic neuropathic pain.

General notes

- Consult local prescribing guidance to confirm first-, second- and third-line treatments. Consult SmPCs or BNF before prescribing.
- Titrate dose according to response and tolerability. Continue drug at full tolerated dose for 2–4 weeks before deciding lack of efficacy.
- When agreeing a treatment plan, discuss the person's concerns and expectations as well as the severity of the pain. A 50% reduction in pain is an appropriate goal.
- Benefits and adverse effects of medication and the importance of the titration process should be explained fully and provided in writing.

Pregabalin*

Caution in heart failure, renal impairment, elderly (dizziness) and suicidal ideation/behaviour. Reduce starting dose in the elderly and in renal impairment (refer to SmPC).

Initial dose 150 mg, in three divided doses ➤ Increase the dose after 7 days to 300 mg per day ➤ Maximum daily dose 600 mg in 2–3 daily doses.

If not effective or tolerated, gradually wean off over a minimum of one week.

Main side effects: Sedation (less than gabapentin), tachycardia, gastrointestinal upset, headache, weight gain (may need diabetes medications increased), mood change and suicidal thoughts.

Gabapentin*

Avoid in patients with history of drug abuse. Caution in people with a history of psychosis or seizures, elderly (dizziness) and suicidal ideation/behaviour. Consider stopping if acute pancreatitis. Reduce dose in renal impairment (refer to SmPC).

Fast titration suitable for young, healthy adults:
Day 1: 300 mg once daily ➤ Day 2: 300 mg twice daily ➤ Day 3: 300 mg three times daily ➤ Maximum dose 1200 mg three times per day (titrate up in 300 mg doses per day).

Slow titration suitable for elderly and frail:
Start at 100 mg nocte ➤ Increase by 100 mg per day, up to a maximum of 1200 mg per day, until pain is reduced.
If side effects occur, slow titration.

If not effective or tolerated, gradually wean off over a minimum of one week.

Main side effects: Sedation (common), mood changes and a small increased chance of suicidal thoughts, which can be observed as early as one week of treatment.

*Before prescribing, carefully evaluate history for drug abuse, and observe patient for signs of abuse and dependence during treatment. Caution when used with opioids. Both drugs are Class C controlled substances.

Duloxetine

Contraindications: Hepatic impairment, severe renal impairment. Do not use in combination with fluvoxamine, ciprofloxacin, enoxacin or MAOIs.

Initial dose 60 mg daily ➤ Increase to 120 mg daily in two daily doses ➤ Additional response after 8 weeks is unlikely. If ineffective, wean off over 1–2 weeks (withdrawal symptoms are common).

Amitriptyline

Contraindications: Severe liver disease, recent myocardial infarction, any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency. Do not use in combination with MAOIs. Cautions: elderly (increased susceptibility to side effects), CVD, glaucoma.

Initial dose 10–25 mg 2 hours before bed (to reduce "hangover effect") ➤ Titrate up by 10–25 mg every 7 days (in practice, recommended to start on amitriptyline 10 mg daily and titrate weekly by 10 mg. Above 50 mg/day, side-effects tend to outweigh benefits) ➤ Trial for 8 weeks. If ineffective, titrate down and wean off over 4 weeks.

Main side effects: sedation.

Capsaicin cream

For patients who wish to avoid or cannot tolerate oral medication (licensed for use for DSPN only under direct specialist supervision).

Dose: pea-sized amount of cream to area 3–4 times per day. Review treatment at 8 weeks.