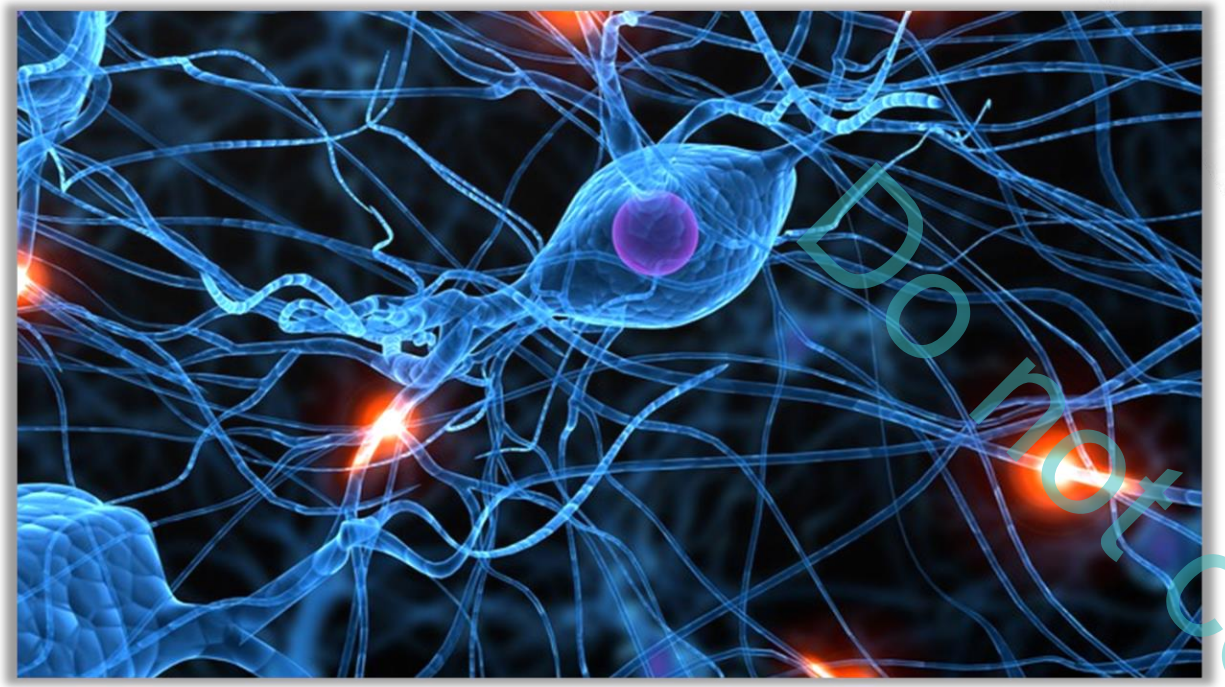

Managing peripheral & autonomic neuropathy in diabetes

19th National Conference of the PCDS
13-14 September 2023

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Disclosures 2023

Speaker fees: Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Dexcom, Daiichi Sankyo, GSK, Lilly, Menarini, Novartis, Novo Nordisk, Roche Diagnostics, Embecta

Advisory Board fees: Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Menarini, Novartis, Novo Nordisk, Roche, Roche Diagnostics, Sanofi

Conference attendance: Menarini, Daiichi Sankyo

Type 2 Diabetes Cardiovascular Renal Metabolic Review Checklist

Medscape UK X Guidelines
Primary Care Hacks

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Consider the following during T2D CVRM shared decision making:

Lifestyle Considerations

- [ ] Assess weight (e.g. BMI or WHR) and discuss individualised weight loss goals as appropriate. Remember to ethnically adjust these goals where indicated[1]
- [ ] Discuss the importance of 24-hour physical behaviours for T2D[2]
  - o sitting/breaking up prolonged sitting
  - o sweating
  - o strengthening
  - o sleep
  - o stepping
- [ ] Strive for remission of T2D if possible,[3] irrespective of weight.[4] Weight loss of 5–10% confers metabolic improvement; weight loss of 10–15% or more can have a disease-modifying effect and lead to remission of T2D[2]

Individualised HbA_{1c} Goals

- [ ] Review the person's current HbA_{1c} and trend, and consider other factors when individualising HbA_{1c} goals, e.g.:
  - o risks potentially associated with hypoglycaemia and other drug adverse effects
  - o life expectancy
  - o comorbidities
  - o established vascular complications
  - o patient preference, resources, and support systems[5]
- [ ] See the expert consensus statement on diabetes and frailty for individualising management in older adults and/or adults with frailty and T2D

Kidneys

- [ ] Individualise HbA_{1c} targets in people with diabetic kidney disease
  - o be aware that all SGLT2is have negligible glucose-lowering effect once eGFR falls below 45 ml/min, so consider adding in an additional glucose-lowering medication such as a GLP-1 RA
- [ ] If eGFR <60 ml/min/1.73 m^2 **or** clinically significant proteinuria (ACR ≥3 mg/mmol) **and** on maximally tolerated dose of ACEi/ARB: consider adding SGLT2i with renal protective benefits,[2] irrespective of HbA_{1c}
  - o see the Primary Care Hack, *Extra-Glycaemic Indications of SGLT2 Inhibitors*
- [ ] If CKD present, offer atorvastatin 20 mg for primary or secondary prevention of CVD[6]
- [ ] Offer aspirin or clopidogrel to adults with CKD for the secondary prevention of CVD,[7] but be aware of the risk of bleeding
- [ ] Consider referral as per NICE criteria, or if 5-year risk of requiring renal replacement therapy is >5% (measured using the Four-Variable Kidney Failure Risk Equation)

Blood Pressure

There is considerable debate around optimal BP targets for people living with diabetes, with several conflicting guidelines published

- [ ] **First instance:** aim for a HBPM average target of <135/85 mmHg (<140/90 mmHg clinic target) in all people[8]
- [ ] **Provided treatment is well tolerated:** then aim for HBPM average of 125/75 mmHg (130/80 mmHg clinic target) or lower in most people[8]
- [ ] **For adults aged >80 years:** consider a clinic BP target of <150/90 mmHg[9]
- [ ] **For people living with T2D:** start drug treatment with an ACEi/ARB,[9] irrespective of age or ethnic background
- [ ] Measure sitting and standing BP in people with hypertension and T2D.[9] In those with a significant postural drop in BP (i.e., ≥20 mmHg systolic and/or ≥10 mmHg diastolic that occurs on standing[10]), treat to a BP target based on the standing BP

Note: SGLT2is have a modest impact on BP, lowering it by around 4/2 mmHg[11]

Lipids

- [ ] LDL-C targets for people living with T2D:[12]
  - o moderate risk: <2.6 mmol/l
  - o high risk: ≥50% reduction from baseline **and** <1.8 mmol/l
  - o very high risk: ≥50% reduction from baseline **and** <1.4 mmol/l
- [ ] Patient's QRISK3 is ≥10%: offer atorvastatin 20 mg for primary prevention of CVD[6][13]
- [ ] If LDL-C targets are not achieved on maximally tolerated dose statin, consider combination lipid-lowering therapy e.g., add in ezetimibe, bempedoic acid, or PCSK9 inhibitor[12]
- [ ] For secondary prevention of CVD, offer atorvastatin 80 mg[12]

Continued overleaf...

NAFLD

- [ ] Noninvasive tests for liver fibrosis risk may be advisable due to the strong association of T2D with NAFLD[14][15][16]
- [ ] Consider FIB-4 test to assess for underlying fibrosis risk in people aged 35–65 years
- [ ] If identified as intermediate or high risk, consider referral to secondary care gastroenterology for transient elastography (FibroScan)
- [ ] Strongly encourage and facilitate weight loss where possible: weight loss 3–5% reduces hepatic steatosis, ≥5–7% can lead to resolution of NASH, and ≥10% improves hepatic fibrosis[17]
- [ ] There is emerging evidence for the benefits of metabolic surgery and GLP-1 RAs, and pioglitazone[2] for NAFLD

Comorbidities and Life Story

- [ ] Consider presence of:
  - o CVD or high risk of CVD:[2][18]
    - ASCVD (i.e. IHD/TIA/stroke/PVD): if present, offer early combination therapy with metformin and an SGLT2i, irrespective of HbA_{1c}[18]
    - all subtypes of HF: if present, offer early combination therapy with metformin and an SGLT2i, irrespective of HbA_{1c}[18]
    - QRISK3 ≥10% and age >40 years, or presence of hypertension, dyslipidaemia, smoking, obesity, or family history (in a first-degree relative) of premature cardiovascular disease: consider early combination therapy with metformin and an SGLT2i, irrespective of HbA_{1c}[18]
  - o CKD and proteinuria[2][18] (see Kidney section)
  - o obesity:[2][17] both SGLT2is and GLP-1 RAs can facilitate weight loss in people living with T2D
  - o retinopathy:[18] be aware of the possibility of worsening of pre-existing retinopathy if HbA_{1c} is rapidly lowered
  - o OSAHS; these conditions are commonly associated with T2D.[2][19] Consider using the Epworth sleepiness scale and the STOP–BANG questionnaire to exclude underlying OSAHS
- [ ] Educate women of childbearing age that many medications (e.g. ACEis, ARBs, statins, SGLT2is, and GLP-1 RAs) are contraindicated in pregnancy, and counsel them regarding contraception.[20][21] If planning pregnancy, refer to pre-pregnancy services
- [ ] Consider age, functional and frailty status, occupation, literacy level, and other social determinants of health during shared decision making[2][7][18]

Prescribing Considerations

- [ ] Discuss adherence and if necessary explore barriers/preferences[2][18][21]
- [ ] Review history of hypoglycaemia/hypoglycaemia awareness, DVLA adherence, and CBG monitoring where appropriate, and consider CGM in all people with T2D on insulin[2][18]
- [ ] Sick-day guidance[20][21]
  - o for people with T2D on insulin
  - o review the SADMANS mnemonic. Consider temporarily pausing these drugs during any significant intercurrent illness, but remind individuals to restart once they are eating and drinking normally and recovered from their illness
- [ ] SGLT2i or GLP-1 RA commenced:
  - o consider reduction in SU or insulin dose. If on insulin, consider cautiously reducing insulin dose, increase CBG monitoring, and contact DSN as required[17][22][23]
  - o consider adjustment of any dose of diuretic when introducing an SGLT2i[20][24][25]
- [ ] Ensure appropriate/optimal prescribing; consider de-intensifying in the context of functional dependence and frailty[26]

MDT Referrals

- [ ] DSMES (e.g. DESMOND or X-Pert)
- [ ] Consider any locally available physical activity referral pathway
- [ ] Regular retinopathy screening
- [ ] Regular foot screening
- [ ] Consider secondary care as required, e.g., diagnostic uncertainty or treatment option advice
- [ ] Consider dietician referral, and psychological counselling for diabetes distress

Coding

- [ ] Code identified conditions as 'priority 1'
- [ ] Do not code 'diabetes resolved'; instead, code 'diabetes in remission'

Follow Up

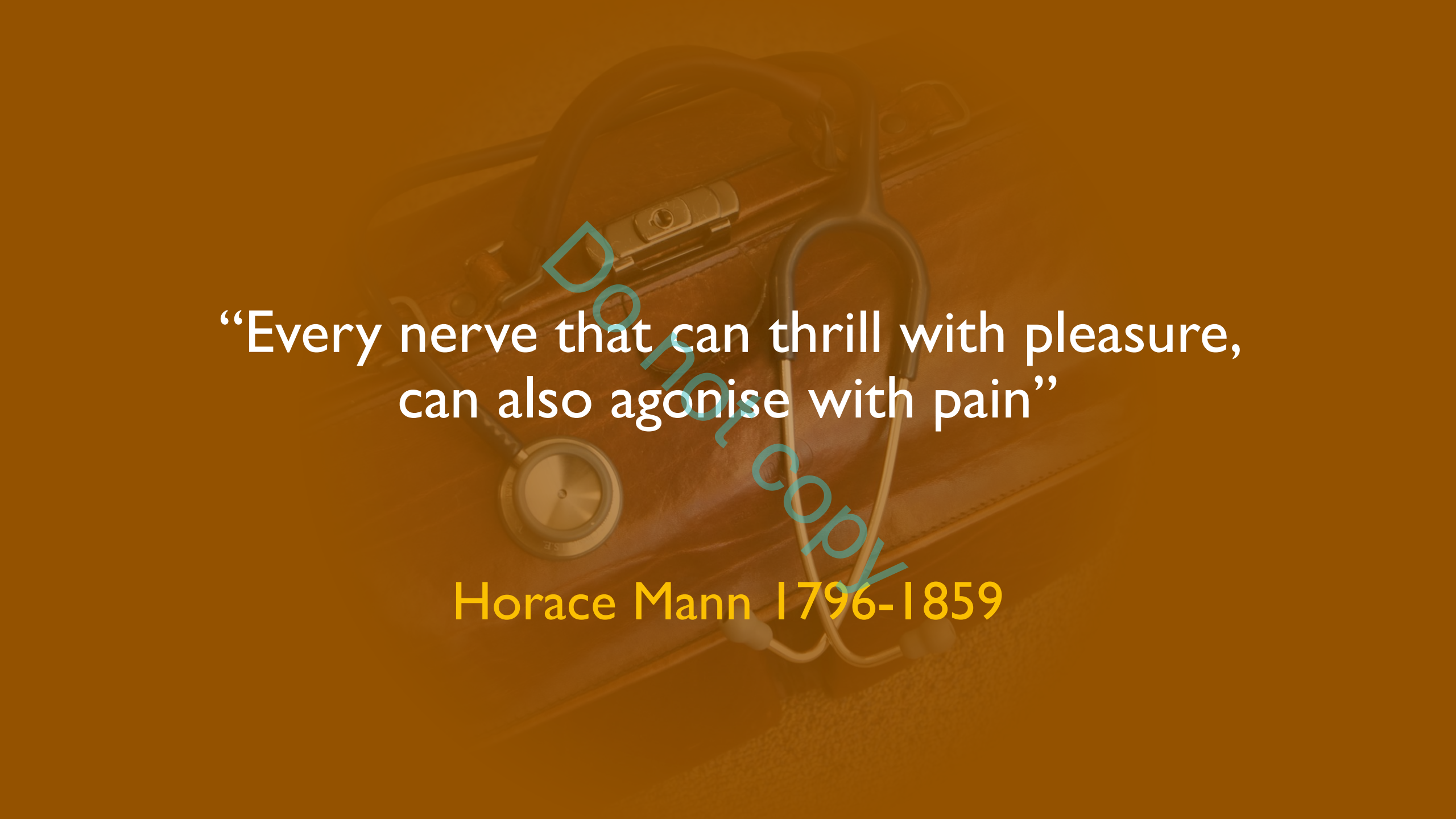
- [ ] Goal setting—Diabetes UK information prescriptions can help to facilitate goal setting, information sharing, and care planning
- [ ] Set a defined timescale for follow up and consider regular monitoring as clinically indicated
- [ ] Regular monitoring of weight, BP, HbA_{1c}, renal function (both eGFR and urinary ACR), and lipid profile as clinically indicated (at least annually).

Abbreviations: **ACEi**=angiotensin-converting enzyme inhibitor; **ACR**=albumin to creatinine ratio; **ARB**=angiotensin receptor blockers; **ASCVD**=atherosclerotic cardiovascular disease; **BP**=blood pressure; **CBG**=capillary blood glucose; **CGM**=continuous glucose monitoring; **CHF**=congestive heart failure; **CKD**=chronic kidney disease; **CVD**=cardiovascular disease; **CVRM**=cardiovascular, renal, and metabolism; **DESMOND**=diabetes education and self-management for ongoing and newly diagnosed; **DSMES**=diabetes self-management, education, and support; **DSN**=diabetes specialist nurse; **DVLA**=Driver and Vehicle Licensing Agency; **eGFR**=estimated glomerular filtration rate; **FIB-4**=Fibrosis-4; **GLP-1 RA**=glucagon-like peptide-1 receptor agonist; **HbA_{1c}**=haemoglobin A_{1c}; **HBPM**=home blood pressure monitoring; **HDL-C**=high-density lipoprotein cholesterol; **HF**=heart failure; **HFpEF**=heart failure with preserved ejection fraction; **HFrEF**=heart failure with reduced ejection fraction; **IHD**=ischaemic heart disease; **LDL-C**=low-density lipoprotein cholesterol; **MDT**=multidisciplinary team; **NAFLD**=nonalcoholic fatty liver disease; **OSAHS**=obstructive sleep apnoea hypopnoea syndrome; **PARS**=Physical Activity Referral Service; **PVD**=peripheral vascular disease; **QRISK3**=Cardiovascular Risk Score 3; **SGLT2i**=sodium–glucose cotransporter-2 inhibitor; **STOP–BANG**=snoring history, tired during the day, observed stop breathing while sleep, high blood pressure, BMI >35 kg/m^2, age >50 years, neck circumference >40 cm, and male gender; **SU**=sulfonylurea; **TIA**=transient ischaemic attack; **T2D**=type 2 diabetes; **WHR**=waist to hip ratio.

For references, view the webpage for this Primary Care Hack at bit.ly/407CT9G

@EimearDarcy @DrKevinFernando @GLNS_Medscape medscape.co.uk/guidelines

Last updated: March 2023



"Every nerve that can thrill with pleasure,
can also agonise with pain"

Horace Mann 1796-1859

Learning Objectives

i. Key take-home messages from OPTION-DM

ii. Practical tips and pitfalls to avoid for the diagnosis & management of peripheral neuropathy

iii. Practical tips and pitfalls to avoid for the diagnosis & management of autonomic neuropathy

THE LANCET

ARTICLES | VOLUME 400, ISSUE 10353, P680-690, AUGUST 27, 2022

Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial

Prof Solomon Tesfaye, MD • Gordon Sloan, MRCP • Jennifer Petrie, BSc • David White, MPH • Mike Bradburn, MSc • Prof Steven Julious, PhD • Prof Satyan Rajbhandari, MD • Sanjeev Sharma, MD • Prof Gerry Rayman, MD • Ravikanth Gouni, MRCP • Uazman Alam, MD • Prof Cindy Cooper, PhD • Amanda Loban, PhD • Katie Sutherland, MSc • Rachel Glover, MSc • Simon Waterhouse • Emily Turton, MA • Michelle Horspool, PhD • Rajiv Gandhi, MD • Deirdre Maguire, MD • Prof Edward B Jude, MD • Syed H Ahmed, FRCP • Prashanth Vas, PhD • Christian Hariman, MBChB • Claire McDougall, MD • Marion Devers, MD • Vasileios Tsatlidis, MD • Martin Johnson, MD • Prof Andrew S C Rice, MD • Prof Didier Bouhassira, PhD • Prof David L Bennett, PhD • Dinesh Selvarajah, PhD • on behalf of the OPTION-DM trial group • Show less

Open Access • Published: August 22, 2022 • DOI: https://doi.org/10.1016/S0140-6736(22)01472-6 •

Check for updates

Keep your OPTIONs open for the treatment of diabetic peripheral neuropathic pain

Diabetic peripheral neuropathic pain (DPNP) is a frequent complication of diabetes and a major cause of morbidity and reduction in quality of life. Despite this, there is little comparative evidence on which analgesic treatment to recommend or whether they should be combined. The aim of the OPTION-DM trial was to establish the most clinically beneficial and best tolerated treatment pathway for people with DPNP. If there was suboptimal pain relief after 6 weeks of monotherapy, participants were assigned to complete three treatment pathways in random order. The investigators demonstrated that each pathway was similarly effective and that combination treatment, where needed, was well tolerated and provided improved pain relief. These findings have the potential to influence the treatment of DPNP in primary and secondary care.

Kevin Fernando
GP in North Berwick

Every nerve that can thrill with pleasure, can also agonise with pain.
Horace Mann (1796–1859)

Neuropathy is one of the most common complications of diabetes. Diabetic peripheral neuropathy affects around half of people living with diabetes over their lifetime and around half again present with diabetic peripheral neuropathic pain (DPNP). DPNP can be debilitating and have a significant impact on quality of life, as well being associated with sleep and mood disorders.

In 2013, NICE published a guideline (CG173) covering the management of neuropathic pain with pharmacological treatments in adults in non-specialist settings. It was last updated during 2020 (NICE, 2020). In it, NICE recommends that for the initial treatment of all neuropathic pain (except trigeminal neuralgia) we should offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin. It also reminds us that pregabalin and gabapentin are Class C controlled substances, and we should remain vigilant to the development of signs of abuse and dependence.

If the initial treatment is not effective or is not tolerated, we should offer one of the remaining three drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

We can also consider tramadol for acute rescue therapy, but not for long-term use. Additionally, capsaicin cream can be considered for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Whilst these recommendations are useful, we lack head-to-head evidence regarding which specific first-line drug to use and whether we should consider drugs in combination when pain relief on monotherapy is ineffective.

OPTION-DM was a UK multicentre, randomised, double-blind, crossover trial that recruited 140 participants with DPNP. Crossover trials compared several treatments; all participants received the same two or more treatments, but in a randomly assigned order. There was usually a washout period between each treatment, during which no treatment was taken. Crossover trials minimise the risk of confounding, as all treatments are assessed in the same participants. Downsides include a risk of aliasing or the impact of the previous treatment on the effect of the next treatment – hence, the appropriate use of washout periods in this study.

Citation: Fernando K (2022) Diabetes Distilled: Keep your OPTIONs open for the treatment of diabetic peripheral neuropathic pain. *Diabetes & Primary Care* **24**: 123–4

- UK multicentre randomised double-blind crossover trial
- 140 participants with DPNP with mean daily pain NRS ≥4
  - Mean age 62y, 130 men, 122 white, majority T2D

- Participants were assigned to 3 different treatment pathways in a random order for 16 weeks:
  - Amitriptyline + pregabalin if needed
  - Pregabalin + amitriptyline if needed
  - Duloxetine + pregabalin if needed
  - Note no placebo group for comparison or P+D pathway

- Monotherapy for 6w then further drug added if pain scores still significant
  - All drugs were titrated up to maximal tolerated dose (up to 75mg/day amitriptyline, 120mg/day duloxetine & 600mg/day pregabalin)
  - 1 week washout period

- Participants followed-up for 1 year
  - 64% completed 2 pathways & 59% completed 3 pathways

- Primary outcome: difference in 7-day average daily pain NRS during the final week of each pathway

- 7-day average pain scores were reduced in all 3 pathways and no significant differences were found between each pathway

- Mean NRS reduction in patients on combination therapy was greater than those on monotherapy

- Improvements in QOL, depression, anxiety & sleep outcomes

“

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy

Paracelsus 1493-1541

TREATMENT PATHWAY (WEEKS 0-16)

ADVERSE EFFECT	A+P	D+P	P+A	P-VALUE
DRY MOUTH	32%	8%	17%	0.0003
DIZZINESS	12%	16%	24%	0.036
NAUSEA	5%	23%	7%	0.011

Reflections

- Amitriptyline, pregabalin & duloxetine similar efficacy as monotherapy
  - Individualise choice according to side-effects & co-morbidities
- Combination therapy provided better pain control than monotherapy
  - Combination therapy should now be standard practice for DPNP
- What is the role of topical medications & opioids for DPNP?
- Is switching from gabapentin to pregabalin sensible given same class?
- What is the role of non-pharmacological interventions for DPNP?

Types of Diabetic Neuropathy

- Peripheral neuropathy
  - Sensory or motor, painful or non-painful

- Autonomic neuropathy
  - Affecting multiple systems – CV, GI, GU, sweat glands
  - More common in females

- Mononeuropathies / mononeuritis multiplex
  - Cranial or peripheral; III nerve palsy must be distinguished from aneurysm or tumour so imaging often required

- Diabetic amyotrophy (proximal motor)
  - Severe pain & numbness upper legs with weakness & muscle wasting of thigh and pelvic girdle muscles
  - Maybe asymmetrical, occasional extensor plantar response, associated dramatic weight loss

Symptoms of Diabetic Neuropathy

- Sensory
  - Negative or positive
  - Diffuse or focal
  - Stocking & glove distribution of extremities
  - Usually insidious onset
    - NB acute peripheral neuritis

- Motor
  - Distal, proximal or focal weakness
  - Sometimes sensorimotor

- Autonomic
  - Varied symptoms involving CV, GI, GU systems & sweat glands

Peripheral Neuropathy

- Diagnosis of exclusion
- "DADRUM"
  - Also consider coeliac screen as per NICE NG20 2015
- Iatrogenic causes:
  - Metronidazole, amiodarone, nitrofurantoin, phenytoin, ciprofloxacin, antiretrovirals, statins
- Consider bloods:
  - FBC, U&E, LFT, ESR, TSH, Ca, Mg, haematinics, ANA & anti-CCP, HbA1C, HIV
- Consider investigations – nerve conduction studies & EMG

Common Mimics of Peripheral Neuropathy

- Intermittent claudication
- Morton's neuroma
- OA
- Radiculopathy
- Charcot neuropathy
- Plantar fasciitis
- Tarsal tunnel syndrome

Autonomic Neuropathy

- Often co-exists with a sensory peripheral neuropathy
- If symptomatic has a poor prognosis; cardiac autonomic neuropathy (CAN) is associated with an increased risk of mortality
- Optimise control diabetes in all
- NB loss of hypoglycaemic awareness NICE NG28 2022
- Diabetic retinopathy is the most significant risk factor predictive of the presence of CAN in patients with type 2 diabetes. J Diab Res 2016

Autonomic Neuropathy

- Cardiac
  - Resting tachycardia, postural hypotension, orthostatic brady- & tachycardia
  - Increased intra-operative or peri-operative CV lability
  - Increased incidence of silent MI, MI, reduced survival after MI
  - Congestive heart failure, exercise intolerance, sudden death

- GI
  - Nausea & vomiting
  - Early satiety/feeling of fullness, abdominal bloating or pain
  - Dysphagia, constipation & diarrhoea especially nocturnal

- GU
  - ED, retrograde ejaculation, urinary hesitancy & overflow incontinence

- Gustatory sweating

Cardiovascular Autonomic Neuropathy

- Check resting pulse & ECG

- Assess for a postural drop in BP (>20mmHg fall abnormal) & abnormal circadian pattern

- Assess heart rate variability with:
  - Deep inspiration
  - Valsalva manoeuvre
  - Change in position from prone to standing

- Management
  - Treatment is symptomatic; refer for specialist advice
  - Avoid rapid changes in posture. Pressure garments
  - Review meds: stop diuretics, vasodilators, TCA which may worsen BP drop
  - Fludrocortisone 50-200mcg daily may help postural hypotension, midodrine 10mg tds (unlicensed in UK), clonidine, ocreotide

Gastrointestinal Autonomic Neuropathy

- Gastroparesis - NICE NG28 2022
  - Consider if erratic blood glucose control or unexplained gastric bloating or vomiting, taking into account possible alternative diagnoses
  - Consider UGIE if possibility of alternative cause for obstructive symptoms

- Advise:
  - Optimising blood glucose control
  - Eat small meals & eat often
  - Lower fat content of meals & consider liquid or homogenised foods

Gastrointestinal Autonomic Neuropathy

- If vomiting, strongest evidence for:
  - Domperidone 10-20mg pre-meals NB MHRA 2014
  - Metoclopramide 5-10mg pre-meals NB EMA 2013
  - Erythromycin 125-500mg pre-meals (azithromycin also a gastric motility agent 500mg od)
  - Consider alternating use of erythromycin & metoclopramide & considering domperidone only in exceptional circumstances

- Refer if diagnosis in doubt or persistent or severe vomiting; patients can be considered for botulinum injection, GES, PEG feeding or surgery

Gastrointestinal Autonomic Neuropathy

- Large bowel involvement – constipation or diarrhoea (especially nocturnal diarrhoea)
- Exclude other causes e.g. IBD, metformin, coeliac, thyrotoxicosis, exocrine pancreatic dysfunction
- For nocturnal diarrhoea, consider high dose codeine 30mg qds, loperamide 2mg qds
  - Erythromycin, tetracycline or metronidazole can sometimes help if bacterial overgrowth
- Consider also somatostatin analogues e.g. ocreotide if secretory/watery diarrhoea

Genitourinary Autonomic Neuropathy

- Erectile dysfunction
  - Full CV screen and manage as usual

- Neuropathic bladder
  - Bladder USS & urodynamic studies; refer urology
  - Advise regular toileting; valsalva to increase bladder contractions
  - Intermittent self-catheterisation or even LTC may be required
  - Consider alpha blocker e.g. tamsulosin 400mcg od

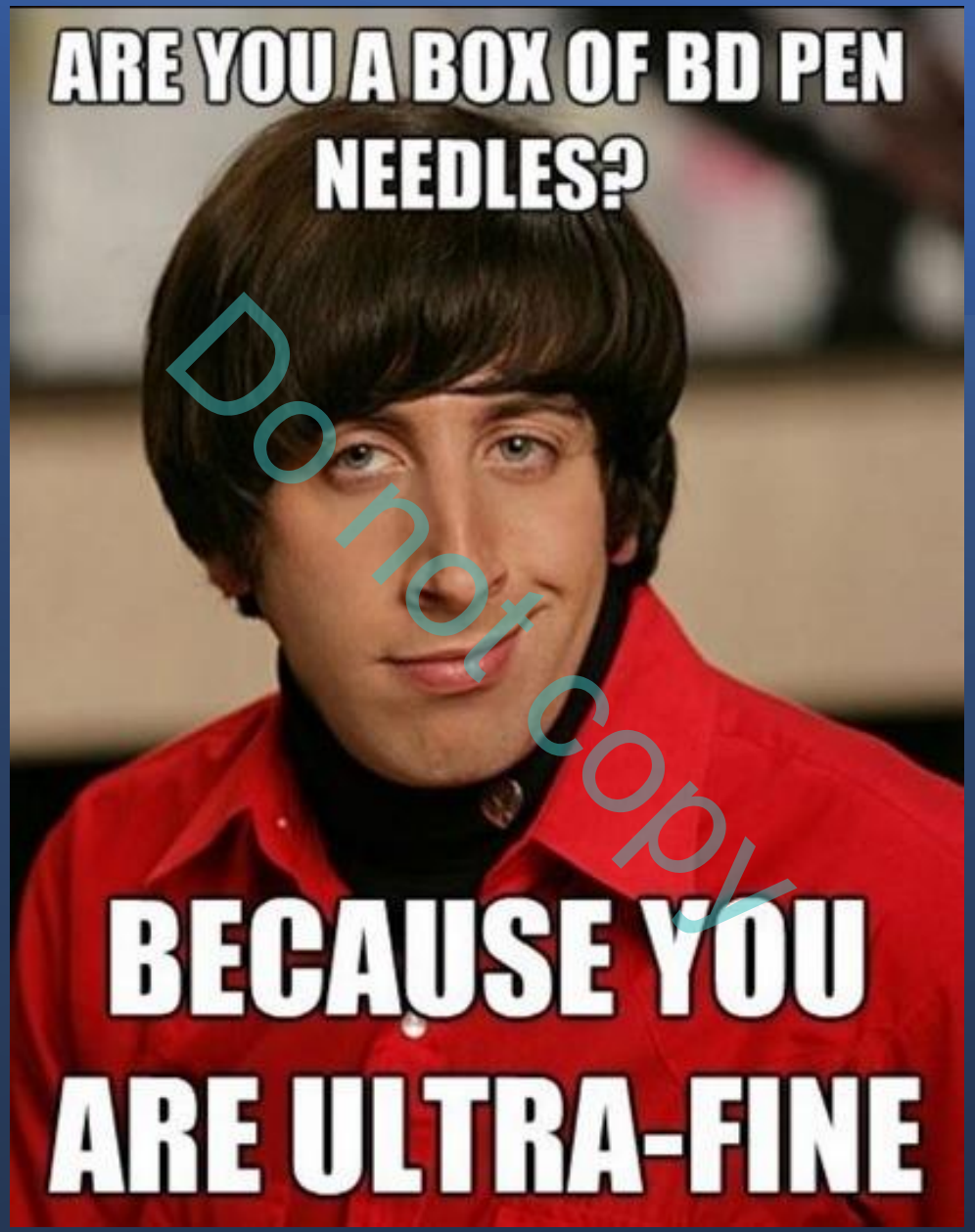
Gustatory Sweating

- Uncommon

- Explanation & counselling are often all that is required; avoid food triggers

- Anticholinergics such as propantheline 15mg tds & 30mg nocte can be helpful or glycopyrronium bromide

- Anhydrosis typically affects feet and is best managed with liberal use of emollients



Thank you for listening & please get in touch if you have any questions

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 Kevin Fernando