

Neuropathic Pain Treatment Guidelines

Background

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic wellbeing. Neuropathic pain is defined as '*pain caused by a lesion or disease of the somatosensory nervous system*'. Central neuropathic pain is defined as '*pain caused by a lesion or disease of the central somatosensory nervous system*', and peripheral neuropathic pain is defined as '*pain caused by a lesion or disease of the peripheral somatosensory nervous system*'.

Neuropathic pain is often difficult to treat because it is resistant to many medications and/or because of the adverse effects associated with effective medications. Pain and anxiety symptoms are subjective with wide variation in reported prevalence. No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patients' responses and diseases, treatment must be individualised. Other than analgesia, factors to consider when individualising therapy include tolerability; other benefits (e.g. improved sleep, mood, and quality of life); co-morbidities; concomitant therapies and contra-indications; low likelihood of serious adverse events and cost effectiveness to the patient and the health economy.

Causes and signs of neuropathic pain

There are various causes and it is often described as burning, stabbing, shooting, aching, tingling, an electric shock or like a sensation of pins and needles. It can be caused by various conditions, which can commonly include the following:

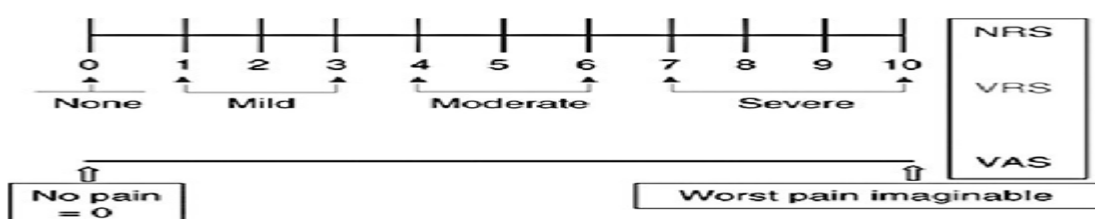
- Trigeminal neuralgia
- Post herpetic neuralgia
- Peripheral Neuropathy (e.g. diabetic, alcohol related, cancer/chemotherapy related)
- Nerve root pain
- Phantom limb pain
- Post-surgical

Assessment

- Exclude serious underlying pathology
- Tools such as DN4 questionnaire (Appendix 1) can be used to detect neuropathic pain

General points

- Chronic neuropathic pain is a long-term condition and the aim of treatment is management rather than cure
- Important to explain implications and chronicity to the patient and the importance of compliance with treatment
- Effective treatment is considered as 30% reduction in pain score and/or improved function
- Always get a pain score as a baseline and following any changes to treatment to enable assessment of benefit. Visual analogue scales are recommended for ease of use



*see below for key

- If no improvement in pain scores do not continue treatment
- Check compliance before making changes to treatment
- REVIEW – trial dose reduction at least 6 monthly to assess ongoing response/need

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NRS: Numeric rating scale

VRS: Verbal rating scale

VAS: Visual analogue scale

Non-pharmacological management and self-help resources

- Encourage self-management and provide education
- Discuss coping strategies for flare up

Treatment Pathway



Tricyclic anti-depressants (TCA)

http://firstport2/resources/patient-info-leaflets/Documents/PIL%20TRICYC.18_18847.L.pdf

Amitriptyline: licensed indication

Imipramine: unlicensed indication but there is a large evidence and practice base to support its use and this is an established indication

Amitriptyline -1st line (Imipramine – if cannot tolerate amitriptyline)

- Start low and go slow
- Start 10mg at night and increase according to response and side-effects
- Increase in 10mg increments with at least weekly intervals
- Initial dose and increments can be decreased to 5mg (half a 10mg tablet) if over-sedation occurs
- Maximum dose 100mg at night (Limited benefits >50mg but increased side-effects)
- Low dose if on concurrent anti-depressant – 25mg
- Contra-indicated in patients with arrhythmias and in the immediate recovery phase following an myocardial infarction
- Use with caution or avoid in the elderly and patients with glaucoma, prostatic hypertrophy or cardiovascular disease
- Dose should be taken at about 8pm but can be taken early evening if hangover effect persists next day
- Particular caution is advised on initiation and after dose increases in patients who drive or operate machinery
- If no response after 4-6 weeks withdraw slowly – usually 10mg at weekly intervals

Increased risk of serotonin syndrome with co-prescribing of tramadol, tricyclic anti-depressants, duloxetine & SSRIs

**Step
2**

- Pain not controlled by TCA or TCA not tolerated or contra-indicated.
- Continue TCA if some pain control or sleep pattern benefit.

Gabapentin

http://firstport2/resources/patient-info-leaflets/Documents/PIL.GABNEU.18_15835.L.pdf

Anti-convulsant drug of choice. Licensed indication for peripheral neuropathy; not licensed for central neuropathy.

- Check renal function and thyroid function prior to commencement
- Dose should be titrated slowly according to response and tolerability (see table 1)
- Dose reduction required in renal impairment (as per SPC – see table 2 below). Renal physician should be contacted where they are involved in patient care
- Note potential for abuse and dependence. Careful consideration before prescribing to patients with a history of substance misuse or recent discharge from prison and in patients co-prescribed opiates. (NOTE interaction between gabapentin and morphine)
- Patient should be assessed for suitability prior to commencement of treatment
- Side effects
 - Initial side-effects are usually minor and subside with 4 weeks
 - Include weight gain and cognitive impairment which includes confusion and memory loss
 - Gabapentin can make patients drowsy or dizzy and occasionally causes severe headaches. Severe headaches do not tend to resolve, treatment should be withdrawn gradually
 - Serious adverse reactions (ADR) are rare

Table 1 - Dose titration

WEEK	8am	2pm	10pm
1	0	0	300mg
2	300mg	0	300mg
3	300mg	300mg	300mg

- Continue on a dose of 300mg three times a day for 4 weeks then assess response; dose can be further increased by 300mg every week to maximum tolerated dose not exceeding 1800mg daily (higher doses up to 3600mg can be used on specialist recommendation)
- For frail/elderly start with 100mg at night and increase by 100mg weekly to a maximum tolerated dose not exceeding 1800mg daily
- If side-effects occur stop titration and remain at tolerated dose for 4 weeks before reassessing and further increasing the dose if required
- Can be restarted at 100mg if 300mg previously not tolerated
- If no benefit after 8 weeks of reaching the maximum tolerated dose, reduce and stop gradually at the same rate as up titration
- Gabapentin was re-classified as a schedule 3 controlled drug from 1st April 2019

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (ml/min) *	Total Daily Dose ^a (mg/day)

≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 ^b -600
<15 ^c	150 ^b -300

^a Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance <79ml/min)

^b To be administered as 300mg every other day

^c For patients with creatinine clearance <15ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15ml/min receive)

* NOTE - Creatinine Clearance (CrCl) is not the same as eGFR unless SA=1.73m². Use Cockcroft-Gault Equation below to calculate CrCl

Ensure step 1/2 drugs have been titrated to maximum tolerated doses and given an appropriate trial period before moving to step 3



Capsaicin 0.075% cream (Axsain[®])

http://firstport2/resources/patient-info-leaflets/Documents/PIL.CAPSAI%2018_18829.L.pdf

- Licensed for painful diabetic neuropathy and post herpetic neuralgia. NICE recommends for localised neuropathic pain where oral treatments are contraindicated or not tolerated
- Non formulary but use is acceptable for patients who require step 3
- Consider for patients with localised neuropathic pain and for patients who wish to avoid or cannot tolerate oral medicines
- A pea sized amount should applied to the affected area 3 or 4 times daily
- Patient should be advised to wash hands immediately after application
- Not to be used on broken or irritated skin
- Needs to be trialled for at least one month before efficacy can be assessed. Discontinue if no benefit
- Note the lower 0.025% strength of capsaicin cream (Zacin[®]) is licensed for pain in osteoarthritis and is not indicated in neuropathic pain

Pregabalin

http://firstport2/resources/patient-info-leaflets/Documents/PIL.PRENEU.18_15835.L.pdf

Pregabalin is licensed in central and peripheral neuropathic pain. SMC restricts use to adults with peripheral neuropathic pain where 1st and 2nd line pharmacological treatments have failed.

- Formulary restriction: only for use where gabapentin has been ineffective or not well tolerated
- Dose should be titrated slowly according to response and tolerability (see table 3)
- Dose reduction required in renal impairment (as per SPC – see table 4 below). Renal physician should be contacted where they are involved in patient care
- Note potential for abuse and dependence. Careful consideration before prescribing to patients with a history of substance misuse or recent discharge from prison and in patients co-prescribed opiates
- Patient should be assessed for suitability prior to commencement of treatment
- Always prescribe as a twice daily dose using the minimum number of capsules possible as this is more cost effective than three times daily dosage
- Side effects
 - Can make patients drowsy or dizzy and may cause confusion
 - Adverse reactions are usually mild to moderate in intensity

Table 3 – Dose Titration

WEEK	morning	night
1	75mg	75mg
2	150mg	75mg
3	150mg	150mg
4	225mg	150mg
5	225mg	225mg
6	300mg	225mg
7	300mg	300mg

- For frail/elderly or drug sensitive patients start with 25mg twice daily and titrate slowly by 25mg weekly to response and tolerability
- If no benefit after 8 weeks of reaching the maximum tolerated dose, reduce and stop gradually at the same rate as up titration
- Treatment should be reviewed 6 monthly and dose should be trial stepped down where pain is controlled
- Pregabalin was re-classified as a schedule 3 controlled drug from 1st April 2019

Table 4 Pregabalin dose adjustment based on renal function

Creatinine clearance (CrCl) (ml/min)*	Total pregabalin daily dose **		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	Twice Daily
≥ 30 - < 60	75	300	Twice Daily
≥ 15 - < 30	25 – 50	150	Once or Twice Daily
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose ⁺

** Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

⁺ Supplementary dose is a single additional dose

* NOTE - Creatinine Clearance (CrCl) is not the same as eGFR unless SA=1.73m². Use Cockcroft-Gault Equation below to calculate CrCl

Cockcroft-Gault Equation

Creatinine Clearance = $\frac{(140 - \text{Age}) \times \text{Body weight (Kg)} \times 1.04 \text{ Females or } 1.23 \text{ Males}}{\text{Serum Creatinine}}$

- For overweight patients Ideal (Lean) body weight should be used

Calculations for Approximation of "Lean" Body weight (Kg)

- For Males Kg = Height (cm) - 100
- For Females Kg = Height (cm) - 105

Switching from Gabapentin to Pregabalin

- Ideally gabapentin should be gradually decreased and stopped before starting pregabalin as this allows the efficacy of gabapentin to be assessed
- If pain worsens on dose reduction then gabapentin is beneficial and should be continued at the lowest effective dose rather than switching to pregabalin
- Patients should be advised that effective treatment is considered as 30% reduction in pain score and/or improved function
- Ensure that pain score is recorded prior to any medication or dose changes

Tramadol (Refer to NHS Lanarkshire Chronic Non Malignant Pain Opioid Prescribing Guideline)

Licensed in moderate to severe pain

Formulary restriction: For short term use in patients who have not obtained adequate benefit from Step 1 and 2 medicines whilst awaiting referral to the Pain Clinic

- +/- 1st and 2nd line choices
- Tramadol + paracetamol may be appropriate if mixed aetiology (prescribe as separate components; Tramacet[®] (tramadol 37.5mg/paracetamol 325mg) is non-formulary and is not approved by the Scottish Medicines Consortium for use within NHS Scotland)
- Schedule 3 controlled drug and classified as a strong opioid
- NOTE: other opiates are not routinely recommended in the treatment of neuropathic pain
- Withdraw gradually if no response after 4 weeks
- Standard capsules should be used in preference to MR or XL products

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Other options

Carbamazepine - (First Line treatment of trigeminal neuralgia)

Licensed in trigeminal neuralgia. Use in diabetic neuropathy is unlicensed.

- Initial dose of 100mg-200mg daily, increasing slowly in increments of 100mg-200mg at weekly intervals according to response
- Usual maintenance dose 600mg-1200mg in 24 hours
- Maximum dose of 1600mg daily
- If ineffective follow neuropathic pain pathway from step 1

Lidocaine 5% medicated plasters (Ralvo[®], Versatis[®])

Licensed for post-herpetic neuralgia only. Non-formulary in NHS Lanarkshire

- Restricted for use in patients who are intolerant of first line systemic therapies for post-herpetic neuralgia or where these therapies have been ineffective
- The painful area should be covered with the plaster once daily for up to 12 hours within a 24 hours period. Only the number of plasters that are needed for an effective treatment should be used. When needed, the plasters may be cut into smaller sizes with scissors prior to removal of the release liner
- Discontinue treatment after 2-4 weeks if no response
- If the patient has responded to treatment and pain is completely alleviated then a plaster-free period should be trialled after 7 days of plaster use
- Treatment should be reassessed every four weeks to decide whether the amount of plasters required to cover the painful area can be reduced, or if the plaster-free period can be extended
- There is a NHS Lanarkshire Lidocaine Medicated Plaster review protocol available on Firstport
- Ralvo[®] is currently the most cost effective brand of lidocaine plasters

Duloxetine

http://firstport2/resources/patient-info-leaflets/Documents/PIL%20DULOXE.18_18830.L.pdf

Licensed for diabetic peripheral neuropathic pain only.

Formulary Restriction: 60mg-120mg daily for treatment of diabetic neuropathy ONLY where treatment with Step 1 and 2 medicines has not provided adequate benefit.

- SMC advice -restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as 2nd or 3rd line therapy
- Start with 30mg daily for 2 weeks and titrate up to a maximum of 120mg daily
- Discontinue if inadequate response after 2 months
- Review at least every 3 months
- Contra-indicated in liver disease and severe renal impairment (CrCl<30ml/min)

Increased risk of serotonin syndrome with co-prescribing of tramadol, tricyclic anti-depressants, duloxetine & SSRIs

APPENDIX 1

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics? YES NO

Burning YES NO

Painful cold YES NO

Electric shocks YES NO

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area? YES NO

Tingling YES NO

Pins and needles YES NO

Numbness YES NO

Itching YES NO

EXAMINATION OF THE PATIENT

QUESTION 3:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics? YES NO

Hypoesthesia to touch YES NO

Hypoesthesia to pinprick YES NO

QUESTION 4:

In the painful area, can the pain be caused or increased by: YES NO

Brushing? YES NO

YES = 1 point NO = 0 points

Patient's Score: /10

A score ≥ 4 is diagnostic of neuropathic pain