Herefordshire and Worcestershire Medicines and Prescribing Committee

NHS
Herefordshire and Worcestershire
Clinical Commissioning Group

Guideline for Pharmacological Management of Neuropathic Pain in Adults in Primary Care

All Neuropathic Pain (excluding Trigeminal Neuralgia)

NICE CG 173[1] recommends amitriptyline, duloxetine, gabapentin or pregabalin as initial treatments. The steps in this guidance are offered in most cost-effective order.

STEP 1. Amitriptyline[2,3]

- 10mg in the evening increasing by 10-25mg every 3-7 days according to effect & tolerability to maximum 75mg
- Duration of adequate trial: 6 – 8 weeks (allow 2 weeks at the maximum tolerated dose)
- Discontinue gradually to prevent discontinuation symptoms (such as dizziness, nausea, anxiety, paraesthesiae diarrhoea, flu like symptoms and headaches).

STEP 2: Gabapentin or Pregabalin[2,3]

Controlled Drug prescription requirements apply. Evaluate patient history of drug abuse before prescribing. See additional notes on page 2.

Gabapentin (Only licensed for peripheral neuropathic pain, other uses would be off-label)[3]

- Start at 300mg at night, titrate upwards by 300mg a week until efficacy achieved, max dose reached or not tolerated. (See Appendix 1 for an example titration regimen). Faster titration may be appropriate for individual patients. Reduced doses required in renal impairment (see Appendix 1).
- Usual Therapeutic Dose Range: 300mg – 3600mg daily in three divided doses.
- Duration of adequate trial: 3 – 8 weeks for titration (allow 2 weeks at maximum tolerated dose)
- Discontinue gradually. See Appendix 1 for instructions on discontinuation.

Pregabalin

- Prescribe generically and start at 75mg twice daily, titrate upwards until efficacy achieved or not tolerated (see Appendix 2 for information on titration). Reduced doses required in renal impairment (see Appendix 2).
- Usual Therapeutic Dose Range: 150 – 600mg daily in divided doses. SPC & BNF specify this can be two to three divided doses. However, in practice, twice daily dosing is most common.
- Duration of adequate trial: 3 – 8 weeks for titration (allow 2 weeks at maximum tolerated dose)
- Discontinue gradually. See Appendix 2 for instructions on discontinuation.

STEP 3: Duloxetine[2,3]

Licensed for diabetic neuropathy, other uses would be off label

- Start at 60mg daily (a 30mg starting dose may be appropriate for some patients). Increase to 60mg twice daily if needed. Avoid if CrCl <30ml/minute and avoid in liver disease resulting in hepatic impairment.
- Duration of adequate trial: 8 weeks (allow at least 4 weeks at maximum tolerated dose)
- Discontinue gradually over a minimum of 1 – 2 weeks to reduce the risk of withdrawal reactions

STEP 4: Combination

- NICE CG 173 does not recommend the use of combination therapy, but BNF[3] states **AMITRIPTYLINE AND PREGABALIN** can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose.

TOPICAL TREATMENTS

- Capsaicin cream 0.0075% (Axsain®) is suggested by NICE[1] as an option for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.
- Licensed uses: symptomatic relief of neuralgia associated with and following Herpes Zoster infections (post-herpetic neuralgia) after open skin lesions have healed, and for the symptomatic management of painful diabetic peripheral polyneuropathy.[4]

- Some treatment options in this guideline are 'off-label' use of licensed medications. Information and advice on prescribers responsibilities when prescribing 'off label' medications can be found at: Off label and Unlicensed Use of Medicines.
- For full prescribing information please see BNF or Summary of Product Characteristics (SPC)
- Paracetamol, alone or in combination with codeine or dihydrocodeine is commonly used but a Cochrane review[5] found insufficient evidence to support or refute that this works in any neuropathic pain condition.

Treatments that should not be used[1]

The following treatments SHOULD NOT BE USED in non-specialist settings unless advised by a specialist to do so.

- Capsaicin Patch (hospital only)
- Lamotrigine
- Levetiracetam
- Morphine
- Oxcarbazepine
- Topiramate
- Venlafaxine
- Sodium Valproate
- Tramadol (long-term use)

Note: NICE[1] recommends **tramadol** can be started in non-specialist settings only if acute rescue therapy is needed. For dosing recommendations, see current British National Formulary (BNF) guidelines.

When to Refer to a Specialist Pain Service[1]

Consider referring to a specialist pain service if

- They have severe pain or
- Their pain significantly limits their lifestyle, daily activities and participation or
- Their underlying health condition causing neuropathic pain has deteriorated

Treatment of Post-herpetic Neuralgia[6]

- Treat initially with standard oral therapies as per **Steps 1 – 4** and/ or **topical capsaicin** (unless contra-indicated or not tolerated).
- If standard therapies fail, or lead to intolerable side effects, consider **lidocaine 5% medicated plasters.**
- Prescribe as the brand RALVO®. Patient Information Leaflet available here. The cost of 30 plasters is £60.
- Prescribe a trial of 2 weeks initially and then review for effectiveness before the medication is continued as a repeat prescription. Lidocaine plasters are approved for primary care initiation only when used to treat post-herpetic neuralgia[7].

Treatment of Trigeminal Neuralgia[1,8]

- **First line: carbamazepine, start at 100mg twice daily** (Prescribe generically and as immediate release preparation). The SPC and BNF recommend increasing gradually according to response with a usual dose of 200 mg 3 – 4 times a day. (MR preparations may be useful at night if the patient experiences breakthrough pain).
- If there is inadequate response or treatment is not tolerated, consider early referral to a specialist pain or condition specific service.
- Once pain is in remission, gradually reduce the dose to the lowest possible maintenance dose.
- **Monitoring:** FBC, U&Es and LFTs at baseline and repeat periodically. Continue monitoring patient for symptoms of blood disorder (e.g. fever, sore throat etc.).
- **See BNF or NICE Clinical Knowledge Summaries[8]** for full information on contraindications, cautions, interactions and adverse effects

Gabapentin and Pregabalin[9]

- From April 2019 both agents have been given a Schedule 3 Controlled Drug status.
- Prescribers should evaluate patients carefully for a history of drug abuse and dependence and observe them for possible signs of abuse and dependence, for example drug seeking behaviour, dose escalation and development of tolerance.
- Patients should be made aware of the risk of potentially fatal interactions with other medicines that CNS cause CNS depression, particularly opioids and with alcohol.

Treatment Plan[1]

A treatment plan should be agreed with the patient taking into account their concerns and expectations.

- the severity of the pain, and its impact on lifestyle, daily activities (including sleep disturbance) and participation
- the underlying cause of the pain and whether this condition has deteriorated
- why a particular pharmacological treatment is being offered

- the benefits and possible adverse effects of pharmacological treatments, taking into account any physical or psychological problems, and concurrent medications
- the importance of dosage titration and the titration process, providing the person with individualised information and advice
- coping strategies for pain and for possible adverse effects of treatment
- non-pharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist pain services). Where possible the patient should have ownership of the titration process and be given sufficient information and support to do this.

General Advice

Patients should be advised that:

- All oral medications in the neuropathic pain algorithm can affect their ability to drive or operate heavy machinery when taken. This may be worse during the initiation period and upward titration of the dose. Patients should be advised not to drive or operate heavy machinery if they feel, for example, that the medication is causing them to feel drowsy, dizzy, unable to concentrate or slower to react than usual. Patients and prescribers are advised to check the DVLA website for the latest information about the laws relating to drugs/medicines and driving.
- All oral medications in the neuropathic pain algorithm carry a risk of developing dependence (psychological or physical) when taken, particularly if they start taking the medication at more frequent intervals or at higher doses than prescribed. If they feel that they need to take the medication in this manner, they must contact the prescriber. The risk can be reduced by ensuring that the patient is regularly assessed by the prescriber and by gradually withdrawing and stopping medication where it is not effective.
- Medications that work initially can stop working in the longer-term so it is important that they alert the prescriber if they feel that their medication is no longer controlling the pain.

Follow Up[1]

- A treatment review date should be scheduled after starting treatment. See algorithm for adequate trial periods under each drug, however for some patients it may be better to schedule this in right at the start.
- Each review should include assessment of:
    - Pain control
    - impact on lifestyle, daily activities (including sleep disturbance) and participation
    - psychological and physical wellbeing
    - adverse effects
    - continued need for treatment
- Titrate medications to maximum tolerated dose and measure the response by assessing the effect of the medication after the suggested trial periods, usually within **6 – 8 weeks** of initiation against the baseline neuropathic pain score and/or baseline function[11].
- At each stage if an improvement in agreed pain relief goal and/or function is not demonstrated after the suggested period of adequate trial, or if the medication is not tolerated, then gradually withdraw and stop before moving to the next appropriate step (see appendix 1 and 2 for GABA reducing regimes).[11]
- If successful, it is suggested that there should be a reduction on an annual basis to ascertain ongoing effectiveness[11].

Pregnancy and Breastfeeding

- Although there is an MHRA alert specifically for sodium valproate/valproic acid in females of childbearing potential, it may be pertinent to have discussions about effective contraception in females of child bearing age when using antiepileptic drugs e.g. gabapentin, pregabalin or carbamazepine in the management of neuropathic pain.
- Information regarding pregnancy and exposure to medicines is available from the UK Teratology Information Service.

References:

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H&W MPC Approved Date: **November 2020**	**Review Date:** **November 2023**

Appendix 1: Gabapentin Regimens

Dose titration. The BNF and SPC suggest an accelerated regimen. In practice, this is limited by side-effects and should be reserved for fit, healthy adults with a clear understanding of the titration and side effects.

Table 1. Gabapentin Titration Regimen (start at 100mg and increase proportionally in elderly or frail patients i.e. those likely to be susceptible to side-effects)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Morning		300mg	300mg	300mg	300mg	600mg
Midday			300mg	300mg	600mg	600mg
Night	300mg	300mg	300mg	600mg	600mg	600mg

MAXIMUM dose: Can be titrated up to **3600mg/day**

DISCONTINUATION: Suggest reducing by 300mg a week until stopped. For those who are likely to be more susceptible to withdrawal e.g. those on high doses, elderly/frail, prescribed >12-months, reduce by 100mg a week in patients. PHE recommends reducing the daily dose at a maximum rate of 300mg every 4 days.

Table 2. Dose Reduction Required In Renal Impairment (as per **SPC**)

CrCl (ml/min)	Total daily dose
≥ 80	900 – 3600 mg/day
50-79	600 – 1800 mg/day
30-49	300 – 900 mg/day
15-29	150 (given as 300mg alt days) – 600 mg/day
< 15	150 – 300mg/day and reduce daily dose in proportion to CrCl e.g. patients with
See information in SPC for patients undergoing haemodialysis or seek specialist advice	

Appendix 2: Pregabalin Regimens

Dose titration: Titration recommendations are based on the BNF and SPC. The regimen should be tailored to each individual patient and amended according to tolerance.

Table 3. Pregabalin Titration Regimen (prescribe generically).

	Day 1, 2, 3	Day 4, 5, 6	Day 7, 8, 9	Day 10 (if necessary)
Morning	75mg	75mg	150mg	300mg
Night	75mg	150mg	150mg	300mg

MAXIMUM dose: Can be titrated up to **600mg/day**

DISCONTINUATION: Suggest reducing by 75mg a week until stopped. For those who are likely to be more susceptible to withdrawal e.g. those on high doses, elderly/frail, prescribed >12-months, reduce by 25mg a week. PHE recommends reducing the daily dose at a maximum of 50 – 100mg per week.

Table 4: Dose Reduction Required In Renal Impairment (as per **SPC**)

CrCl (ml/min)	Starting dose	Maximum Dose
≥ 60	**75mg BD**	**300mg BD**
≥30-<60	**25mg OM + 50mg ON**	**150mg BD**
≥15-<30	**25mg – 50mg ON**	**75mg BD**
< 15	**25mg ON**	**75mg ON**
See information in SPC for patients undergoing haemodialysis or seek specialist advice		

PREGABALIN can cause QT prolongation

NOTE: Pregabalin is "flat priced" across the dose ranges, therefore increase the strength of the capsule rather than simply increasing the number taken.