# **Management of neuropathic pain (adults) Template pathway**

**Organisations can use this guidance as a template to develop their own local guidance in partnership with key stakeholders such as pain consultants, GPs, pharmacists, nurses and other healthcare professionals.** **Local neuropathic pain treatment pathway discussions should include consideration of: the preferred order of use of first line treatments (if more than one is suitable for the individual patient); treatment costs; whether combination therapies are supported and at what position in the treatment pathway; which treatments are supported for prescribing in primary care, specialist settings only and other locally agreed parameters.**

This template has been developed to support prescribers in a stepwise approach to the management of neuropathic pain and includes a flow chart and additional treatment notes.

The NICE Clinical Guideline for Neuropathic pain in adults: pharmacological management in non-specialist settings [CG173] recommends to:

*“Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)”*.1

Several of the treatment options considered in NICE CG173 are not licensed for all forms of neuropathic pain, but have been used in clinical practice for many years and have an established role in the treatment of neuropathic pain.1 NICE CG173 recommends that the GMC good practice in prescribing and managing medicines and devices (2013) guide is followed when treating neuropathic pain.1,2 This states:

*“You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.”*

*“When prescribing an unlicensed medicine, you must:*

*a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy,  
b. take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so,  
c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.”*

## Information for patients about the licence for their medicines

*“Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population. You must always answer questions from patients (or their parents or carers) about medicines fully and honestly.”*

A PrescQIPP (template) patient information leaflet is available for prescribers to use as an aid to discuss the unlicensed status of some medicines prescribed in neuropathic pain and then give to the patient as a reminder of the information discussed.

The NICE clinical guideline on the management of neuropathic pain in adults [CG173] did not include a recommendation on combination therapy, but did acknowledge that combination therapy is commonly used in practice and may be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain.1 The algorithm reflects this need and proposes that combination therapy is an option before specialist referral.

### Neuropathic pain algorithm

* If a treatment is not licensed for the prescribed indication ensure the patient understands the unlicensed status of the medicine, and has been given patient information and gives informed consent.
* Consider co-morbidities, side effects and potential for dependence and abuse before commencing treatments.
* Consider use of questionnaires (e.g. PainDETECT or LANSS) to identify if neuropathic pain is likely and the type of neuropathic pain.
* Agree an achievable pain relief goal (e.g. 30-50% pain relief or ability to undertake global activities).
* Advise the patient on the medication, titration regimen (see drug specific information below) and target dose.
* Prescribe on acute prescriptions (not repeat) until treatment is stabilised.
* Be aware of serious interactions with opioids (e.g. respiratory depression). Prescribing should be closely monitored due to significant abuse potential.
* Titrate medications to the maximum tolerated dose. If there is no useful response after an adequate trial e.g. eight weeks, or the medication is not tolerated, reduce and stop the medicine before replacing/moving to the next step. Tapering the dose will minimise the risk of discontinuation symptoms.1,3
* When introducing a new drug, consider overlapping it with the old treatment to avoid deterioration in pain control.1 Taper the dose of the drug to be withdrawn to prevent any discontinuation symptoms.3
* The tricyclic antidepressants (TCAs), amitriptyline and nortriptyline, should be withdrawn gradually over about 4 weeks or longer if withdrawal symptoms emerge.4 Withdrawal effects may occur within 5 days of stopping treatment with antidepressants. Symptoms are usually mild and self-limiting, but in some cases may be severe.4
* The dose of duloxetine should be reduced over at least one to two weeks. The most common withdrawal symptoms from duloxetine are nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances and tremor.4
* Gabapentin should be discontinued gradually over a minimum of one week in accordance with current clinical practice.5
* Pregabalin should be withdrawn over at least one week and abrupt withdrawal avoided.4
* The Clinical Knowledge Summary (CKS) on depression provides advice on switching from a TCA to a different TCA or to another type of antidepressant.6 A direct switch from amitriptyline to nortriptyline is possible.6
* Switching from amitriptyline/nortriptyline to duloxetine requires cautious cross-tapering starting with low dose duloxetine.6
* Assess the need for continued treatment at each review, including the possibility of gradually reducing the dose if sustained improvement is observed.1
* Discontinue treatments that are ineffective even if there is no alternative medication available. If discontinuation is not acceptable, consider reducing dosages.
* Refer to the ‘Treatment review and deprescribing’ information (page 11) andthe data on the individual drugs (pages 5-10) for recommendations on duration of discontinuation.
* Refer to the individual manufacturers summary of product characteristics (SPCs) for monitoring of side-effects and dosage adjustments required in renal and hepatic impairment.

**Figure 1. Neuropathic pain treatment pathway (can be adapted locally)**

|  |
| --- |
| **Trigeminal neuralgia** |
| Use carbamazepine first line for trigeminal neuralgia |
|  |
| **All other types of neuropathic pain: follow treatment pathway below** |
| **Amitriptyline**  10mg-75mg at night  **OR if treatment effective but not tolerated consider:**  Nortriptyline 10mg-75mg at night (use 3 x 25mg tablets for 75mg dose) |
| If not tolerated or inadequate response, **replace with** |
| **Duloxetine**  60mg-120mg once daily |
| If not tolerated or inadequate response, **replace with** |
| **Gabapentin**  300mg-1200mg three times daily  **OR**  **Pregabalin**  150mg-600mg daily in two or three divided doses  (twice daily dosing is preferred to three times daily dosing)  Switch to the one which was not used first (gabapentin or pregabalin) if not tolerated or there is an inadequate response |
| If not tolerated or inadequate response, **consider** |
| Combination therapy with two agents from different classes where some response was seen.  **OR**  Topical treatment (capsaicin 0.075% cream applied sparingly) for localised neuropathic pain and for patients who wish to avoid or cannot tolerate oral medicines. |
| If not tolerated or inadequate response:  **STOP and refer** |
| Refer to pain clinic for specialist assessment if there is inadequate response to treatment or treatments not tolerated.  Whilst patient is awaiting assessment by specialist, consider adding short term treatment with tramadol (50-100mg every 4 to 6 hours up to a maximum of 400mg/24 hours) for acute rescue therapy only. |

**Do not start the following treatments in non-specialist settings**:

* Cannabis sativa extract
* Capsaicin patch
* Lacosamide
* Lamotrigine
* Levetiracetam
* Lidocaine plasters (except in post-herpetic neuralgia)
* Morphine
* Oxcarbazepine
* Topiramate
* Tramadol - long term
* Venlafaxine

# **Prescribing notes**

### For trigeminal neuralgia only: Carbamazepine (first line)

**Notes**

* Initially 100mg, using immediate release preparations, (once daily or divided into twice daily dose) increased gradually according to response. Usual dose 200mg three to four times daily, up to 1.6g total daily dose in some patients.4
* If ineffective, follow neuropathic pain pathway from step 1 (below).

**For sciatica**

Do not offer pregabalin, gabapentin, other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm. Do not offer opioids for managing chronic sciatica.7

### For all other neuropathic pain

**Step 1**

**Amitriptyline**

Amitriptyline is licensed for the treatment of neuropathic pain in adults.4

Titrate amitriptyline slowly to reduce the side effects:4

* Typical starting doses are 10mg-25mg at night. The dose should be gradually increased according to the patient’s response and tolerance, usually every 3-7 days in 1 or 2 divided doses. Usual dose is 25–75 mg daily.4
* Advise the patient to take the dose in the evening.4
* Caution in mild-to-moderate hepatic impairment; avoid in severe impairment.4
* Drowsiness may affect the performance of skilled tasks, e.g. driving.4
* The effects of alcohol are enhanced with amitriptyline.4
* An example amitriptyline titration dosage regimen is given in table 1 below - doses taken at night. Ensure the patient tolerates the dose at each step before increasing further.

**Table 1. Amitriptyline dose titration**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 |
| 10mg | 20mg | 30mg | 40mg | 50mg | 75mg |

* If amitriptyline is not effective or not tolerated, discontinue treatment gradually over a minimum of 4 weeks to prevent discontinuation symptoms (such as dizziness, nausea, paraesthesiae, anxiety, diarrhoea, flu-like symptoms, and headaches).3

**Nortriptyline**

* Nortriptyline (unlicensed use) may be considered if amitriptyline is not tolerated, but effective.4
* Avoid in severe hepatic impairment.4
* The CKS on depression provides advice on switching from a TCA to a different TCA.6 A direct switch from amitriptyline to nortriptyline is possible.6
* An example direct switch from amitriptyline to nortriptyline is given in table 2 below. This can be adapted to suit an individual’s tolerability.

**Table 2. Example switching regimen for amitriptyline to nortriptyline**

|  |  |  |
| --- | --- | --- |
|  | **Pre-switch dosage** | **Week 1** |
| **Withdrawing amitriptyline** | 75mg daily | Nil |
| **Introducing nortriptyline\*** | Nil | 75mg daily |

\*Avoid using the more costly nortriptyline 50mg tablets.8

**Step 2**

## Duloxetine

## Duloxetine is licensed for diabetic peripheral neuropathic pain only, so use for other conditions is off label.4

## In secure environments duloxetine is recommended for consideration prior to prescribing gabapentin or pregabalin due to the risk of abuse and diversion of these medicines.9

* Avoid use in hepatic impairment and if eGFR is less than 30mL/minute/1.73m2.4

## The dose is 60mg once daily, increased to a maximum of 120mg daily in divided doses.4

## Treatment should be discontinued after two months if there is an inadequate response. Treatment should be reviewed at least every three months for continued need.4

## When discontinuing duloxetine or reducing the dose (for intolerance or ineffectiveness), gradually reduce the dose over a minimum of 1 to 2 weeks in order to reduce the risk of withdrawal reactions.4

* Switching from amitriptyline or nortriptyline to duloxetine requires cautious cross-tapering starting with low dose duloxetine.6 An example cross-tapering regimen switching from amitriptyline to duloxetine is given in table 3. This can be adapted locally and also to suit an individual’s tolerability.

**Table 3. Example switching regimen for amitriptyline/nortriptyline to duloxetine**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pre-switch dosage** | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** |
| Withdrawing amitriptyline / nortriptyline | 75mg daily | 50mg daily | 40mg daily | 25mg daily | 10mg | Nil | Nil |
| Introducing duloxetine | Nil | 30mg daily | 30mg daily | 60mg daily | 60mg daily | 60mg daily | 60mg twice daily (if needed for pain relief) |

**Step 3**

## Gabapentin

## Gabapentin is licensed for peripheral neuropathic pain and postherpetic neuralgia in adults.3,5 NICE recommends gabapentin as a first-line treatment option for adults with all neuropathic pain, except trigeminal neuralgia.1

## Generic gabapentin capsules are the most cost-effective formulation of gabapentin.8 Where appropriate for patients with a current low tablet/capsule load, using multiples of the 100mg, 300mg or 400mg strength capsules to make up a dose should be considered, but this can be complicated. Gabapentin should be started slowly. Table 4 gives an example dose titration regimen for gabapentin (usually suitable for otherwise healthy younger adults).3,5

## Table 4. Gabapentin dose titration

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Increasing every 2-3 days until tolerated\* | Increasing every 2-3 days until tolerated\* |
| Morning |  | 300mg | 300mg | 300mg | 300mg | 600mg | 600mg |
| Midday |  |  | 300mg | 300mg | 300mg | 300mg | 600mg |
| Night | 300mg | 300mg | 300mg | 300mg | 600mg | 600mg | 600mg |

## \*Usually 2-3 days but may take up to a week in some patients.3

## Once a patient is on a 900mg daily dose, the dose can be increased in 300mg increments every two to three days until tolerated. The dose should be increased to either the dose that provides sufficient pain relief or the maximum tolerated dose. The maximum daily dose is 3600mg.5

## The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of two weeks, and to reach 3600 mg/day is a total of three weeks.5

## Be aware of the risk of CNS depression, including severe respiratory depression. Consider whether dose adjustments might be necessary in patients at higher risk of respiratory depression, including elderly people, patients with compromised respiratory function, respiratory or neurological disease, or renal impairment, and patients taking other CNS depressants.5

* Recommended dosage adjustments in renal impairment are given in table 5 below.5

**Table 5. Gabapentin dose titration in people with renal impairment**

|  |  |  |
| --- | --- | --- |
| **Renal function (eGFR)/ mL per minute per 1.73 m2** | **Starting dose**  **(to be administered as three divided doses)** | **Maximum daily dose**  **(to be administered as three divided doses)** |
| 50-79 mL per minute per 1.73 m2 | 600mg | 1800mg |
| 30-49 mL per minute per 1.73 m2 | 300mg | 900mg |
| 15-29 mL per minute per 1.73 m2 | 300mg on alternate days | 600mg |
| <15 mL per minute per 1.73 m2 | 300mg on alternate days | 300mg |

In renal impairment, the elderly or frail dose titration may need to be done in 100mg increments.3,5

## If there is no improvement within eight weeks of reaching the maximum tolerated therapeutic dose, consider deprescribing and use pregabalin as an alternative treatment.3

## Gabapentin should not be stopped abruptly and should be reduced gradually over a minimum of one week, depending on dose and duration of treatment.3

## In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than five months. If a patient requires dosing longer than five months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.5

## Cases of abuse have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of gabapentin abuse.5

An example cross-tapering regimen switching from duloxetine to gabapentin is given in table 6. This can be adapted locally and also to suit an individual’s tolerability.

**Table 6. Example switching regimen from duloxetine to gabapentin**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pre-switch dosage** | **Day 1** | **Day 2** | **Days 3 & 4** | **Day 5** | **Day 6** | **Day 7** | **Then every 2 to 3 days** |
| **Withdrawing duloxetine** | 120mg daily | 60mg daily | 60mg daily | 60mg daily | 30mg daily | 30mg daily | Nil | Nil |
| **Introducing gabapentin** |  |  |  |  |  |  |  |  |
| **Morning** | Nil | 300mg | 300mg | 300mg | 300mg | 600mg | 600mg | Increase gabapentin dose by 300mg every 2-3 days until maximum tolerated dose or a maximum of 3600mg per day taken |
| **Midday** | Nil | Nil | Nil | 300mg | 300mg | 300mg | 600mg |  |
| **Night** | Nil | Nil | 300mg | 300mg | 600mg | 600mg | 600mg |  |

## Pregabalin

* Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.4
* Pregabalin should be started slowly and titrated to response.4
* Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.4 An example initiation dosage regimen is given in table 7 below.

**Table 7. Pregabalin dose titration**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Day 1 until tolerated | Day 3-7 until tolerated | Day 14 |
| Morning | 75mg | 150mg | 300mg |
| Night | 75mg | 150mg | 300mg |

* Pregabalin should not be stopped abruptly but should be reduced gradually over a minimum of one week.3
* Recommended dosage adjustments in renal impairment are set out in table 8.4

**Table 8. Pregabalin dose titration in people with renal impairment**

|  |  |  |
| --- | --- | --- |
| **Renal function (eGFR)/ mL per minute per 1.73m2** | **Starting dose** | **Maximum daily dose** |
| 30-60ml per minute per 1.73m2 | 75mg a day (in two to three divided doses | 300mg a day (in two to three divided doses) |
| 15-30 ml per minute per 1.73m2 | 25 to 50mg a day (in one dose, or two divided doses) | 150mg a day (in one dose, or two divided doses) |
| <15 ml per minute per 1.73m2 | 25mg once a day | 75mg once a day |

An example **cross-tapering regimen switching from duloxetine to pregabalin** is given in table 9 below. This can be adapted locally and also to suit an individual’s tolerability.

**Table 9. Example switching regimen for duloxetine to pregabalin**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre-switch dosage** | **Day 1 to 6** | **Day 7** | **Day 14** |
| **Withdrawing duloxetine** | 120mg daily | 60mg | 30mg | Nil |
| **Introducing pregabalin** | Nil | 75mg twice daily | 150mg twice daily | 300mg twice daily |

## Step 4

## Capsaicin 0.075% cream

## Capsaicin 0.075% cream (Axsain®) is licensed for the symptomatic relief of postherpetic neuralgia after open skin lesions have healed, and for the symptomatic relief of painful diabetic neuropathy (only under the direct supervision of a hospital consultant who has access to specialist resources).3

## Advise the person to apply a small amount of cream (pea size) to the affected area 3–4 times a day (not more often than every 4 hours).3

**Combination therapy**

**[Local decisions on whether combination therapy should be included in the local pathway need to be made. The NICE CKS on neuropathic pain states “Do not prescribe more than one neuropathic pain drug at the same time.3]**

* Combination therapy is commonly used in practice and may be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs.1
* Be aware of the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed together. Prescribers should be aware of the increased risk of side effects and also drug interactions when two drugs are prescribed together.4

**Tramadol (acute rescue therapy only)**

* Whilst the patient is awaiting assessment by specialist pain management services, consider adding short term treatment with tramadol (50-100mg every 4 to 6 hours up to a maximum of 400mg/24 hours) for acute rescue therapy only.1
* Prescribe tramadol cautiously due to the potential for misuse.3
* Tramadol is a Schedule 3 controlled drug and is licensed for moderate to severe pain.4

**Treatment review and deprescribing**

The table below provides information of when treatment should be reviewed, how treatment should be deprescribed and the potential discontinuation symptoms for each of the drugs included in the neuropathic treatment pathway.1,3-5,10-12

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Treatment review** | **Withdrawal period** | **Potential discontinuation symptoms** |
| Amitriptyline | After 6 to 8 weeks, with at least 2 weeks at the maximum tolerated dose | Gradually reduce over 4 weeks | Dizziness, nausea, paraesthesiae, anxiety, diarrhoea, flu-like symptoms and headaches |
| Duloxetine | Initial response: Up to 8 weeks  Review every 3 months | Gradually reduce over a minimum of 1 to 2 weeks | Nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances and tremor |
| Pregabalin | 4 weeks | Gradually reduce over a minimum of 1 week. A more gradual reduction of a maximum of 50-100mg/week allows observation of emergent symptoms that may have been controlled by the drug. | Insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness |
| Gabapentin | After 3 to 8 weeks with at least 2 weeks at the maximum tolerated dose | Gradually reduce over a minimum of 1 week. A more gradual reduction of a maximum of 300mg every four days allows observation of emergent symptoms that may have been controlled by the drug. | Anxiety, insomnia, nausea, pains, sweating |
| Capsaicin 0.075% cream | After 8 weeks | Can be withdrawn immediately |  |
| Tramadol | For acute rescue therapy only e.g. 4 weeks | Withdraw gradually to avoid abstinence symptoms | Agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms |

## The deprescribing algorithm below may be used to accompany any decisions to review and deprescribe any neuropathic pain treatments.

# **Deprescribing drugs for neuropathic pain**

For a patient taking drug treatment for neuropathic pain (e.g. amitriptyline, duloxetine, gabapentin, pregabalin, capsaicin cream), do any of the following apply?

* The indication is not documented or valid.
* The treatment is no longer effective.
* The treatment is now contraindicated.
* The patient has requested a reduction in medicine burden.
* The patient is experiencing intolerable side effects.
* An attempt to reduce the dosage has not been undertaken in the last 12 months.
* The patient is over-ordering medicines and may be abusing the medicine or taking a dose outside therapeutic range.

**Yes**

**No**

**Yes**

**Consider deprescribing the neuropathic pain treatment**

* Gradually withdraw treatment to prevent any withdrawal symptoms.
* If more than one drug is prescribed, reduce one at a time.
* Provide neuropathic pain patient information leaflet.

**Does harm outweigh the benefits?**

* Do the potential adverse drug reactions (ADRs) outweigh the possible benefits?
* Patient has a history of substance abuse.
* Patient has co-morbidities which could cause problems with therapy.
* Drug is being prescribed off-label where suitable licensed alternatives exist.
* There is renal or hepatic impairment requiring dosage reduction or treatment cessation.

**No**

Continue prescribing the drug treatment for neuropathic pian with regular review, to ensure that the expected outcome is achieved and no ADRs or contraindications have developed.

## References

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