East Lancashire Health Economy Medicines Management Board
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# Management of neuropathic pain (adults)

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]

## 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 until effective pain control or the maximum tolerated dose is reached. 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overlapping it with the old treatment to avoid deterioration in pain control.[1] Taper the dose of the drug to be withdrawn to prevent any discontinuation symptoms.[3]
- The tricyclic antidepressants (TCAs), should be withdrawn gradually over about 4 weeks or longer if withdrawal symptoms emerge.[4] Withdrawal effects may occur within 5 days of stopping treatment with antidepressants.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 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 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**

| **Trigeminal neuralgia** |
|---|
| Use carbamazepine first line for trigeminal neuralgia |

| **All other types of neuropathic pain: follow treatment pathway below** |
|---|
| **Amitriptyline**<br>10mg-75mg at night |
| If not tolerated or inadequate response, **replace with** |
| **Duloxetine**<br>60mg-120mg once daily |
| If not tolerated or inadequate response, **replace with** |
| **Gabapentin**<br>300mg-1200mg three times daily<br>**OR**<br>**Pregabalin**<br>150mg-600mg daily in two or three divided doses<br>(twice daily dosing is preferred to three times daily dosing)<br>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** |
| 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:<br>**STOP and refer** |
| Refer to pain clinic for specialist assessment if there is inadequate response to treatment or treatments not tolerated.<br>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
- Venlafaxine
- Levetiracetam
- Lidocaine plasters (except in post-herpetic neuralgia)
- Morphine
- Oxcarbazepine
- Topiramate
- Tramadol - long term

## 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]

## 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/1.73m$^2$.[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 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 potential 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]

The BNF suggests an accelerated titration regimen i.e. starting at 300mg three times per day and increasing by 300mg every 2-3 days according to response. In practice this regimen is limited by side effects, therefore it should be reserved for use in a restricted patient group, of particularly fit, healthy adults who have a clear understanding of the titration process and potential side effects, including drowsiness which may affect their ability to drive.

**Table 4. Gabapentin dose titration is generally healthy younger adults.**

| | 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]

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

- **Recommended dose titration for frail/elderly is given below.**

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---|---|---|---|---|---|---|---|
| Morning | | | | 100mg | 100mg | 100mg | 100mg |
| Midday | | | | | | | 100mg |
| Night | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg |
| | **Day 8** | **Day 9** | **Day 10** | **Day 11** | **Day 12** | **Day 13** | **Day 14** |
| Morning | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg | 200mg |
| Midday | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg | 200mg |
| Night | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg | 200mg |
| | **Day 15** | **Day 16** | **Day 17** | **Day 18** | **Day 19** | **Day 20** | **Day 21** |
| Morning | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg |
| Midday | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg |
| Night | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg |

**Day 22 onwards:** Dose may be increased by 300mg/day, ideally at weekly intervals as tolerated up to a maximum of 3600mg

- **Recommended dosage adjustments in renal impairment are given in the table below.[5]**

| Renal function (eGFR)/ mL per minute per 1.73 $m^2$ | 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 $m^2$ | 600mg | 1800mg |
| 30-49 mL per minute per 1.73 $m^2$ | 300mg | 900mg |
| 15-29 mL per minute per 1.73 $m^2$ | 300mg on alternate days | 600mg |
| <15 mL per minute per 1.73 $m^2$ | 300mg on alternate days | 300mg |

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 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]
- In healthy younger individuals 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 below.

**Table 7. Pregabalin dose titration in younger otherwise healthy individuals.**

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

- **In frail/elderly individuals a more cautions slower titration should take place as suggested below.**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** |
| **Morning** | 25mg | 25mg | 25mg | 25mg | 25mg | 25mg | 25mg |
| **Night** | 25mg | 25mg | 25mg | 25mg | 25mg | 25mg | 25mg |
| | **Day 8** | **Day 9** | **Day 10** | **Day 11** | **Day 12** | **Day 13** | **Day 14** |
| **Morning** | 50mg | 50mg | 50mg | 50mg | 50mg | 50mg | 50mg |
| **Night** | 50mg | 50mg | 50mg | 50mg | 50mg | 50mg | 50mg |
| | **Day 15** | **Day 16** | **Day 17** | **Day 18** | **Day 19** | **Day 20** | **Day 21** |
| **Morning** | 75mg | 75mg | 75mg | 75mg | 75mg | 75mg | 75mg |
| **Night** | 75mg | 75mg | 75mg | 75mg | 75mg | 75mg | 75mg |
| | **Day 22** | **Day 23** | **Day 24** | **Day 25** | **Day 26** | **Day 27** | **Day 28** |
| **Morning** | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg |
| **Night** | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg | 150mg |
| **Day 29 onwards:** 300mg twice daily | | | | | | | |

- 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 1.73m$^2$ | Starting dose | Maximum daily dose |
|---|---|---|
| 30-60ml per minute per 1.73m$^2$ | 75mg a day (in two to three divided doses | 300mg a day (in two to three divided doses) |
| 15-30 ml per minute per 1.73m$^2$ | 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 1.73m$^2$ | 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]

### 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

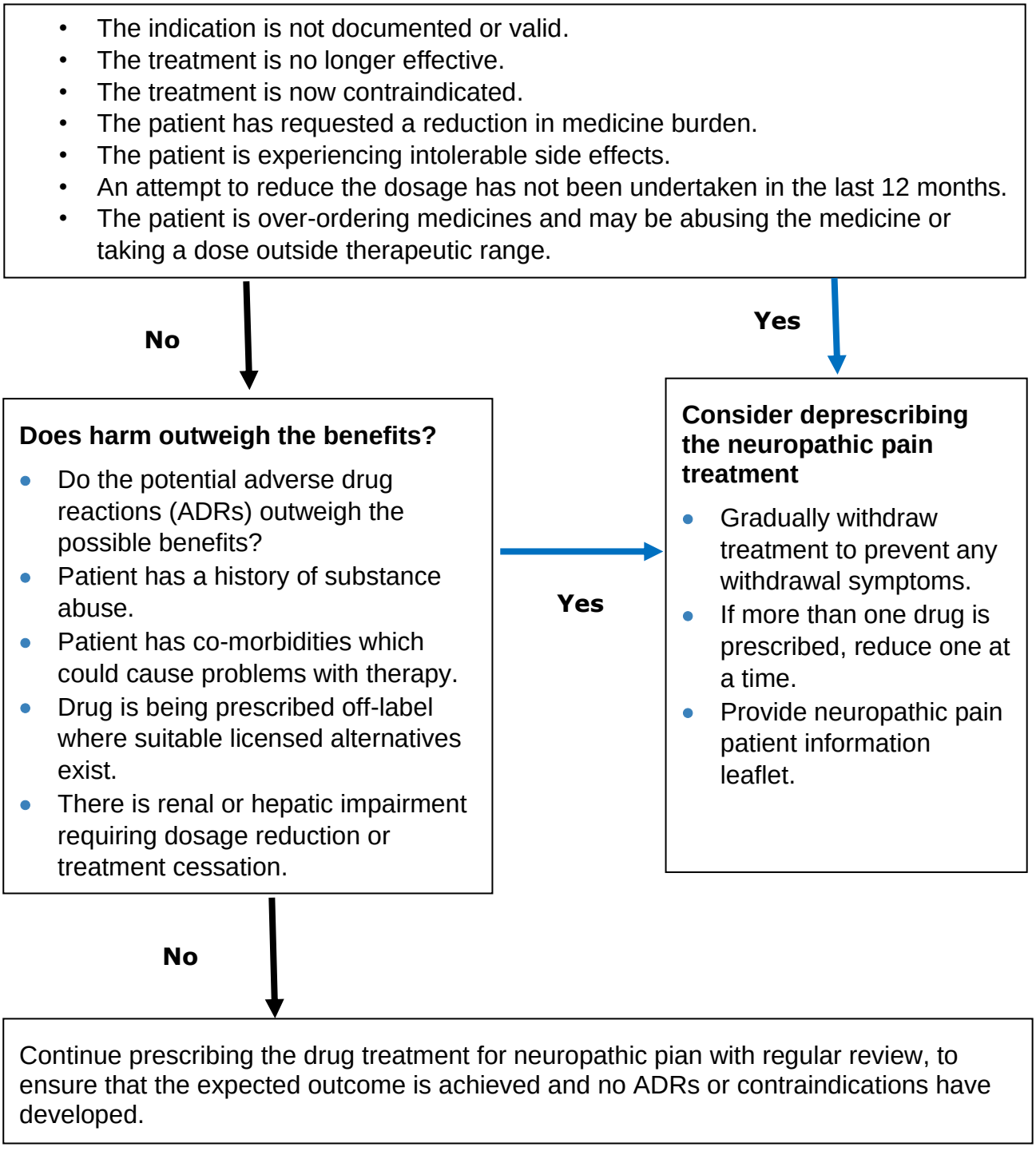
The table below provides information of when treatment should be reviewed, how treatment should be deprescribed and the potential discontinuation symptoms for each of the drugs included in the neuropathic treatment pathway.[1,3-5,10-12]

| 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<br>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?

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