

**Guideline for the treatment of neuropathic pain
for adults in Primary Care**

Version:	V1 (September 2015)
Ratified by:	Northern Lincolnshire Area Prescribing Committee
Date ratified:	24 th September 2015
Updated:	
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Date reviewed:	
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Date issued:	30 th September 2015
Review date:	September 2017
Target audience:	Pain clinic, secondary care and General Practitioners

INTRODUCTION

Neuropathic pain is caused by continuous or previous damage to the nerves, it relates to painful and sensory symptoms caused by lesions in the nervous system. The damaged nerves become hyper excitable and continue to activate the nervous system even though the initial damage has repaired, this can be caused by surgery, trauma and some medical conditions including; Phantom limb pain, painful diabetic neuropathy, post-herpetic neuralgia, complex regional pain syndrome and Trigeminal neuralgia.

Diagnosis

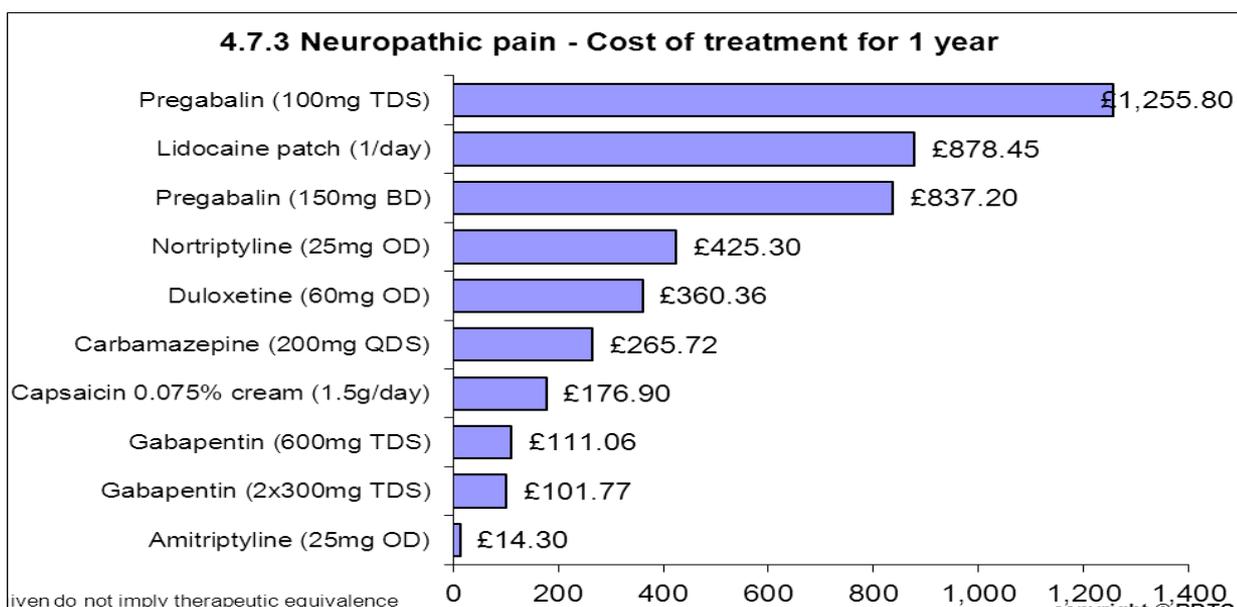
Symptoms are often difficult for patients to describe but may include; Shooting, stabbing, burning, tingling, tight, numb, prickling, and itching and the sensation of pins and needles.

The LANSS pain assessment tool can be found via http://www.meduniwien.ac.at/phd-iai/fileadmin/ISMED/Literaturhinweise/Bennett_LANSS_Pain_001_92.pdf and Appendix 1

Key Recommendation

- If a treatment is not licenced for the prescribed indication, ensure the patient understands the unlicensed status of the medication, and has been given patient information and gives informed consent.
- Consider co-morbidities, side-effects and potential for abuse before commencing treatment(s).
- Prescribe on acute prescriptions (not repeat) until treatment is stabilised.
- Review all treatments after 8 weeks once the dose is titrated to an adequate dose. Discontinue treatments that are ineffective (withdrawal from treatment should be gradual)
- On-going review: treatment should be reviewed regularly for continued need. Discontinue repeats for medication no longer being taken.
- Ensure that gabapentin and pregabalin are prescribed at an appropriate place in therapy for neuropathic pain taking into consideration value for money.
- Ensure prescribed (and taken) doses of pregabalin and gabapentin are not outside the therapeutic dose range. Prescribing of pregabalin capsules should be optimised to the minimum number per dose with a twice daily frequency.
- Patients with a history of substance misuse or those recently released from prison should be given careful consideration before being prescribed pregabalin and gabapentin. Treatment should be reviewed regularly.
- NICE Clinical guideline 173 states “Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)”. Pregabalin and duloxetine are recommended as initial treatment options due to their wider licences, however the full guideline for CG173 acknowledges that both these treatments represent poor value for money and should not routinely be used first in the treatment pathway.
- Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia).

Costs and Savings



Algorithm

Evidence of neuropathic pain

**Trigeminal neuralgia –
First line - Use
Carbamazepine**

Amitriptyline 10 -75mg at night

If not tolerated or inadequate response replace with

Gabapentin 300-3600mg/day

If not tolerated or inadequate response replace with

Duloxetine 60-120mg/day
Or
Pregabalin 150mg-600mg/day
If first choice not tolerated or ineffective
discontinue and try other drug

If not tolerated or inadequate response

Consider combination therapy with two agents from
different classes where some response was seen.

If not tolerated or inadequate response: STOP and refer

Refer to pain clinic for specialist assessment if inadequate
response to treatment or treatments not tolerated. Whilst
patient is awaiting assessment by specialist, consider adding
short term treatment with Tramadol for acute rescue
therapy only

Do not start the following treatments in non-specialist settings

Cannabis sativa extract
Capsaicin patch
Lacosamide
Lamotrigine
Levetiracetam

Morphine
Oxcarbazepine
Topiramate
Tramadol-long term
Venlafaxine

Recommendation/ Patient reviews

- Ensure all patients currently being prescribed pregabalin and gabapentin are done appropriately; as algorithm (Page 3)
- Ensure prescribed (and taken) dose of pregabalin and gabapentin is not outside the therapeutic range.
- Where pregabalin and gabapentin are being prescribed outside of their licenced indication for other non-neuropathic pain, review the need to continue treatment.
- Review all patients prescribed pregabalin to ensure that the minimum number of capsules are issued i.e. two 50mg capsules to one 100mg capsule and that the frequency is optimised to a twice daily frequency. Please see Appendix 2
- Consider switching patients whose neuropathic pain is not controlled on pregabalin to either amitriptyline or gabapentin, if these drugs have not been previously issued and titrated to the maximum therapeutic dose
- Review patient records for compliance – patients requesting ad hoc prescriptions and not taking the medication regularly will not benefit from the treatment, such patients may benefit from PRN (when required) use of other types of analgesia such as paracetamol or NSAIDs.

Trigeminal neuralgia only: Carbamazepine (first line)

- This is one of several antiepileptics that can be of use for trigeminal neuralgia in addition to the tricyclic antidepressants and gabapentin etc.
- Initially 100mg (once 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.
- If ineffective follow neuropathic pain pathway from step 1.

For all other neuropathic pain

Step 1 – Amitriptyline

- Amitriptyline is unlicensed for use in neuropathic pain but there is a large evidence and practice base to support its use and this is an established indication.
- Typical starting doses are 10mg-25mg at night and should be gradually increased according to the patient's needs. Doses above 50mg are seldom required although up to 75mg may sometimes be tolerated. Pain relief may be seen after 1-7 days but it may take two to six weeks for the drug to be effective.
- Advise patient to take at about 8pm; if morning sedation is problematic the dose may be taken earlier in the evening.
- Particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
- A typical amitriptyline dosage regimen:
 - Step 1: - 10mg at night* for 1 week
 - Step 2: - 20mg at night* for 1 week then evaluate response
 - Step 3: - 30mg at night*
 - Step 4: - 40mg at night*
 - Step 5: - 50mg at night*

* Ensure patient tolerates dose at each step before increasing dose.
After step 2 the dose can be increased gradually according to tolerance and the patient's needs.
- If amitriptyline is not tolerated or is ineffective it should be withdrawn gradually over 1-2 weeks and gabapentin tried.

Step 2 –Gabapentin

The anticonvulsant drug of choice is gabapentin (licensed indication for peripheral neuropathy, not licenced for central neuropathy). Capsules are the most cost-effective formulation. Where appropriate for patients with a low tablet/capsule load, using multiple capsules to make up a dose should be considered. Gabapentin should be started slowly according to the regimen below. In renal impairment, the elderly or drug sensitive patients, this titration may need to be done in 100mg increments. Refer to the SPC for more details. Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.

A typical dosage regimen for gabapentin

For neuropathic pain dose range is 900mg to 3600mg daily (dose reduced in renal impairment). Treatment can be initiated at a dose of 900mg/day given as three equally divided doses or at a slower rate as described below:

Step 1: Gabapentin 300mg once daily on day 1.

Step 2: Gabapentin 300mg twice daily on day 2.

Step 3: Gabapentin 300mg three times daily on day 3.

Slower titration of gabapentin may be appropriate for individual patients to improve tolerability.

Once a patient is on a 900mg 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, however in practice many patients do not go over a dose of 1800mg.

An example of a dose increase regimen is shown below:

Step 4: Gabapentin 300mg morning and 300mg mid-day + 600mg night until tolerated.*

Step 5: Gabapentin 600mg morning and night and 300mg mid-day until tolerated.*

Step 6: Gabapentin 600mg morning, 600mg mid-day and 600mg night until tolerated.*

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

The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

Side effects are usually minor and subside within 4 weeks.

Gabapentin can make patients drowsy or dizzy and occasionally causes severe headaches. Severe headaches do not tend to resolve, treatment should be reduced gradually. Serious adverse effects are rare.

If there is no improvement within 8 weeks of reaching the maximum tolerated therapeutic dose, consider alternative treatment. Gabapentin should not be stopped abruptly and should be reduced gradually over a minimum of 1 week, depending on dose and duration of treatment.

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 5 months. If a patient requires dosing longer than 5 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.

Step 3: Duloxetine or Pregabalin

Duloxetine

This can be considered a third line treatment for neuropathic pain (licensed for the treatment of diabetic neuropathy only) in patients who have not achieved adequate pain relief from, or who have not tolerated, first and second line treatments i.e. with amitriptyline or gabapentin. 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.

- The dose is 60mg once daily, increased to a maximum of 120mg daily in divided doses.
- Treatment should be discontinued after 8 weeks if there is an inadequate response.
- Treatment should be reviewed at least every three months for continued need

Pregabalin

Current NHS England guidance (March 2015) is that Pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name Lyrica® (unless there are clinical contraindications or other special clinical needs e.g. patient allergic to an excipient, branded product unavailable etc which apply to Lyrica®, when you should not prescribe Lyrica® or pregabalin).

Pregabalin is an alternative to gabapentin in patients who have not achieved adequate pain relief from, or have not tolerated, first and second line treatments. This drug can be used in combination with a tricyclic anti-depressant, but it should not be co-prescribed with gabapentin (note there may be some crossover when titrating treatments at change of therapy). 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 pregabalin abuse.

- Pregabalin is licensed for neuropathic pain.
- Pregabalin should be started slowly and titrated to response and tolerability as detailed below.
- The dose must be reduced in renal impairment and may need to be reduced in older people, or drug sensitive patients.
- Twice daily dosing is more cost-effective than three times a day dosing.
- Pregabalin can make patients drowsy or dizzy and may cause confusion.

Dose range is 150mg to 600mg daily (reduce dose in renal impairment).

A typical dose regimen for pregabalin:

- Pregabalin 75mg morning and night until tolerated (usually 3 to 7 days), if a dose increase is needed use
- Pregabalin 150mg morning and night until tolerated (after 7 days), if a further dose increase is needed use
- Pregabalin 300mg morning and night until tolerated- no further dose increase is recommended as 600mg daily is the maximum dose.

The starting dose may need to be reduced in drug sensitive or elderly patients. A suitable starting dose may be 25mg twice daily (morning and night). This should be titrated slowly to response and tolerability. Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.

Dosage reduction is required in patients with compromised renal function. Refer to the SPC for details.

Pregabalin should be stopped if the patient has not shown sufficient benefit within 8 weeks of reaching the maximum tolerated therapeutic dose and referred to the Pain Clinic. It should not be stopped abruptly but should be reduced gradually over a minimum of 1 week.

Review long term use and assess the need to continue treatment.

References

- NICE CG 173 Neuropathic Pain – pharmacological management: November 2013
<http://publications.nice.org.uk/neuropathic-pain-pharmacological-management-cg173>
- PrescQIPP Bulletin 50; January 2014; v2.0: Neuropathic pain: Pregabalin and gabapentin prescribing <http://www.prescqipp.info/pregabalin-in-neuropathic-pain/viewcategory/202>
- Prescqipp bulletin 9: Dose optimisation of Pregabalin <http://www.prescqipp.info/pregabalin-in-neuropathic-pain/finish/202-pregabalin-in-neuropathic-pain/266-bulletin-9-pregabalin-dose-optimisation-archive>
- Medicines complete <https://www.medicinescomplete.com/mc/bnf/current/>
- Summary of Product Characteristics <http://www.medicines.org.uk/emc/>

Appendix 1

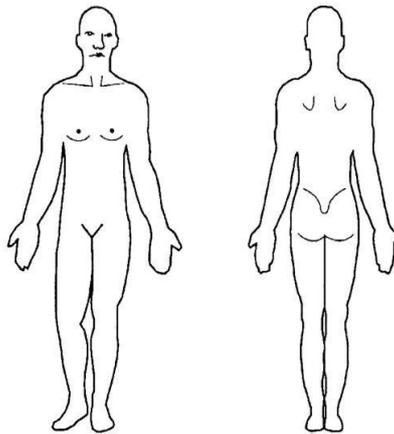
APPENDIX

THE S-LANSS PAIN SCORE

Leeds Assessment of Neuropathic Symptoms and Signs (self-complete)

NAME _____ DATE _____

- This questionnaire can tell us about the type of pain that you may be experiencing. This can help in deciding how best to treat it.
- Please draw on the diagram below where you feel your pain. If you have pain in more than one area, **only shade in the one main area where your worst pain is.**



- On the scale below, please indicate how bad your pain (that you have shown on the above diagram) has been in the last week where:
'0' means no pain and '10' means pain as severe as it could be.

NONE 0 1 2 3 4 5 6 7 8 9 10 SEVERE PAIN

-
- On the other side of the page are 7 questions about your pain (the one in the diagram).
 - Think about how your pain that you showed in the diagram has felt **over the last week**. Please circle the descriptions that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels.
 - Only circle the responses that describe your pain. **Please turn over.**

S-LANSS

- 1. In the area where you have pain, do you also have ‘pins and needles’, tingling or prickling sensations?**
 - a) NO – I don’t get these sensations (0)
 - b) YES – I get these sensations often (5)

- 2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?**
 - a) NO – The pain does not affect the colour of my skin (0)
 - b) YES – I have noticed that the pain does make my skin look different from normal (5)

- 3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.**
 - a) NO – The pain does not make my skin in that area abnormally sensitive to touch (0)
 - b) YES – My skin in that area is particularly sensitive to touch (3)

- 4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like ‘electric shocks’, jumping and bursting might describe this.**
 - a) NO – My pain doesn’t really feel like this (0)
 - b) YES – I get these sensations often (2)

- 5. In the area where you have pain, does your skin feel unusually hot like a burning pain?**
 - a) NO – I don’t have burning pain (0)
 - b) YES – I get burning pain often (1)

- 6. Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?**
 - a) The painful area feels no different from the non-painful area (0)
 - b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area (5)

- 7. Gently press on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?**
 - a) The painful area does not feel different from the non-painful area (0)
 - b) I feel numbness or tenderness in the painful area that is different from the non-painful area (3)

Scoring: a score of 12 or more suggests pain of predominantly neuropathic origin

Appendix 2 – Pregabalin Dose Optimisation

TDS Regime	Alternative BD regime	Capsule Strength
25mg TDS	25mg BD or 50mg BD	Use 1x 25mg capsule per 25mg dose; Use 1X 50mg per 50mg dose
50mg TDS	75mg BD	Use 1X 75mg capsule per 75mg dose
75mg TDS	100mg BD or 150mg BD	Use 1x100mg capsules per 100mg dose; Use 1x 150mg capsules per 150mg dose
100mg TDS	150mg BD	Use 1x 150mg per 150mg dose
150mg TDS	225mg BD	Use 1x 225mg dose
200mg TDS	300mg BD	Use 1X 300mg capsule per 300mg dose