SEL Pharmacological Management of Neuropathic Pain in Adults in primary care

All patients should be reviewed at 8 weeks (unless otherwise stated) after treatment has been started to establish ongoing need to continue

1st line

***AMITRIPTYLINE**

Initiate dose at 10mg/night and **gradually up-titrate as tolerated at 2-4 week intervals** up to 25mg/night to allow acclimatisation of potential side-effects. Doses >25mg/night should usually be on the advice of a specialist. Trial for **12 weeks** then review.

Relative contraindications to therapy include: *recent myocardial infarction, arrhythmia, history of prostatism, or narrow angle glaucoma.*

If this is contra-indicated, or ineffective/not tolerated after trial period, **stop and replace with 2nd line treatment.** If duration of treatment < 6-8 weeks, withdrawal effects unlikely. If duration of treatment > 6-8 weeks, wean off over 4 week period.

Amitriptyline dosing Instructions

- Counsel patient that it can take up to 12 weeks to achieve a therapeutic response.
- Advise patient to take 1-2 hours before bed; if morning sedation is problematic, the dose may be taken earlier in the evening.
- If excessive hangover effect or sedation is an issue, only in this instance should *NORTRIPTYLINE tablets be considered, using the same dose instructions as amitriptyline.

2nd line

****GABAPENTIN**

See dosing titration schedule. Based on patient's response, gradually titrate up (most achieve max pain relief below 2700mg/day) if renal function normal (see product SPC for dosing guidance in renal impairment). Stop when patient reaches pain relief goals, or experiences intolerable side effects. Advise patients that they may not feel pain relief straightaway, as they are building tolerability to the medication.

If this is contra-indicated, ineffective or not tolerated, **stop and replace with 3rd line treatment.**

Gabapentin dosing titration schedule

	Week 1	Week 2	Week 3	Week 4
Morning	100mg	200mg	300mg	400mg
Midday	100mg	200mg	300mg	400mg
Night	100mg	200mg	300mg	400mg

Consider gradual titration in week 1 starting with 100mg at night on Day 1, slowly titrating to 100mg three times daily by Day 5. Max 3600mg/day
Side effects (mainly cognitive) often limit dose incrementation. Consider asymmetrical dosing (more in evening than daytime) if these occur.

3rd line

****PREGABALIN**

Start dose at 50mg TWICE DAILY (see product SPC for dosing guidance in renal impairment) and titrate upwards depending on patient's response. Stop when patient reaches treatment goals or experience side effects. Max. dose is 300mg twice daily.

OR

DULOXETINE - *1st line for neuropathic pain in diabetic peripheral neuropathy but avoid in severe renal impairment (CrCl <30ml/min). Consider amitriptyline instead.*

Starting dose 30mg DAILY - based on patient's response, gradually titrate upwards to 120mg daily (in two divided doses). Response should be seen within 2-4 weeks. Review patient at 8 weeks after initiation and every 3 months thereafter to establish ongoing need to continue. If ineffective at 8 weeks, discontinue treatment.

If this is contra-indicated, ineffective or not tolerated, go onto **combination therapy (4th line)**

Cross tapering from gabapentin to pregabalin/duloxetine

- When cross tapering from gabapentin → pregabalin ***or*** gabapentin → duloxetine, the dose of gabapentin should be reduced by 300mg every 4 days until patient is on 300mg three times daily.
- Gabapentin dose should continue to be withdrawn, whilst commencing 3rd line treatment (see page 3 for further information).
- For dose initiation and titration schedules for pregabalin and duloxetine, please refer to Appendix 2.

4th line

Combination therapy

Check for possible drug interactions – see BNF

Although there is limited evidence for combination therapy, NICE advises using two agents from different classes ahead of considering specialist referral, as it may be helpful if initial drugs were insufficient at reducing pain. May also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs ***e.g. sleep is improved with amitriptyline but if suboptimal pain control, add in gabapentin instead of increasing amitriptyline dose.***

REFER to Specialist Pain Service if all of the above fails or earlier if response is poor.

Include relevant drug history when referring to pain service (see Prescribing Points on next page).
Consider **TRAMADOL only for acute rescue therapy** if needed whilst awaiting referral.
Long term use of tramadol should be only under the advice of a specialist.

NB: *Caution in using duloxetine and tramadol together - potential for increased serotonergic effects (see BNF).*
*Tramadol and paracetamol combination products should **not** be prescribed (see SEL IMOC position statement).*

Localised neuropathic pain

For management of localised neuropathic pain including superficial, small fibre neuropathies, post herpetic neuralgia and painful diabetic peripheral polyneuropathy, consider:

CAPSAICIN 0.075% CREAM (recommended for patients who wish to avoid/cannot tolerate oral treatments). Apply a pea-sized amount up to 4 times daily for 6-8 weeks, then review.

Treatment only to be initiated in specialist care/pain clinic

RED listed (all prescribing in hospital only):

- Topical capsaicin 179mg (8%) patch
- Nabilone*
- Ketamine oral solution*
- Botulinum toxin type A for focal neuropathic pain

AMBER 2 listed (initiation in hospital only):

- Opioids *e.g. Morphine, Oxycodone, Tapentadol*
- Antiepileptics for refractory neuropathic pain *e.g. Lamotrigine*, Topiramate*, Oxcarbazepine** *see GP Information Sheet for more information.*
- **LIDOCAINE 5% (700mg) PLASTERS** (AMBER 2) for treatment of ***post-herpetic neuralgia*** or ****focal neuropathic pain with allodynia.*** Following stabilisation, continuation in primary care should involve an individual management plan. The specialist must specify duration of treatment and clear directions for reviews. See product SPC and SEL IMOC position statement.

For further information, please refer to the SEL Joint Formulary.

Trigeminal neuralgia

CARBAMAZEPINE – Start dose at 100mg twice daily and slowly titrate the dose based on response in steps of 100 - 200 mg every 2 weeks until pain is relieved. Maximum dose is 1600mg daily. See also MHRA updated safety advice on antiepileptic drugs in pregnancy.

If carbamazepine is inappropriate, ineffective, or not tolerated**,** seek specialist advice. Do ***not*** offer any other drug treatment (e.g. oxcarbazepine [AMBER 2 listed]) unless advised to do so by a specialist.

For further information, please refer to **NICE CKS** on trigeminal neuralgia.

*Licensed medicines being recommended for off-label use

Please see PHE guidance on pregabalin and gabapentin use leading to dependence and potential abuse **PHE-NHS England Pregabalin and Gabapentin Advice Dec 2014

South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London: South East London Clinical Commissioning Group (covering the boroughs of Bexley/Bromley/Greenwich/Lambeth/Lewisham and Southwark) and GSTFT/KCH/SLAM/ & Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust.

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Prescribing Points

- When initiating treatment, the prescriber should agree a plan with the patient and provide them with a British Pain Society leaflet (see page 3).
- The 10-point Numeric Rating Scale (NRS) is a pain assessment scale which can be used to measure baseline pain and subsequently to assess whether treatment is effective (see Appendix 1).
- The anticholinergic burden (ACB) of the patient's current medication should be assessed before starting treatment using ACB scales, where a score is assigned to each drug based on its anticholinergic potency. The higher the score, the greater the anticholinergic effect. **The South London and Maudsley Anticholinergic Effect on Cognition (AEC) scale** (available as a web-based app at www.medichec.com) is the preferred ACB scale to use, as its development is more robust and evidence based compared to other ACB scales. Using this feature, prescribers can determine AEC score of a particular medication, add each medication to a list to calculate the total score and email a summary or export as a PDF.
- Caution with concomitant use of opioids in relation to potential sedative and cognitive side effects. Gabapentinoids are opioid-sparing due to synergistic effect meaning less opioid is effectively needed with combined use – opioid dose reduction may be advised to reduce risk of respiratory depression, accidental drug overdose or death (see MHRA advice). Risk of harm with opioids increases substantially at doses above oral morphine equivalent of 120mg/day. Take caution regarding the dependency-forming nature of opioids, regular review required - see SEL IMOC Pharmacological Management of Adult Non-Cancer Chronic Pain in Primary care for more information.
  See also - Guidance for healthcare professionals on drug driving.
- Realistic goals need to be set, as pain free status is not usually achievable and 20-50% reduction in pain is a commonly used end-point in clinical trials.
- The goal of neuropathic pain treatment is to support initial symptomatic relief for people so that they are sufficiently able to engage in non-pharmacological treatment such as light exercise, physiotherapy, relaxation techniques and rehabilitation. NHS exercise advice, including exercise videos, can be accessed at https://www.nhs.uk/live-well/exercise/free-fitness-ideas/
- Consider referral to a dietician for advice on blood sugar control in patients with diabetic peripheral neuropathy.
- Aim to trial amitriptyline for total 12 weeks where possible, then review. For all other steps, trial on maximum tolerated dose for **8 weeks (or earlier where relevant)** for evidence of benefit before moving to the next step. During this time, patients should be encouraged to engage with non-pharmacological strategies as listed above.
- **Clinical review *(at 8 weeks or earlier if applicable)* should include:**

▪ Assessment of pain reduction and adverse effects	▪ Mood (in particular, possible depression and/or anxiety)
▪ Daily activities and participation (such as ability to work and drive)	▪ Overall improvement as reported by the patient
▪ Quality of sleep	▪ Whether there is a continued need for treatment

- **Referral to specialist pain service** should be considered at any stage if:
  - Patient has severe pain *or*
  - Pain significantly limits their daily activity and participation *or*
  - Their underlying health condition has deteriorated.
- On the GP referral form to the pain service, **information on what drug treatment (pharmacological and non-pharmacological) has been trialled so far in primary care** should be included. This should outline:
  - Drug history of what patient has trialled so far *(including dose and strength of treatment)*
  - Whether drug treatment was successful or not
  - Dose at which drug treatment was discontinued, and reason for discontinuation *(where relevant)*
- Appendix 3 shows example of good practice on the level of information that should be provided as standard within clinic letters from the pain service team to GP practices for patients who have been started on treatment for neuropathic pain.
- Pharmacological therapy should not be considered a long-term management strategy and efforts should regularly be made to reduce the dosage and gradual withdrawal of treatment, particularly as many treatments are associated with safety or dependence issues following long-term use.
- At any step when the pain is in **remission** *(remain pain free for 8 weeks)* after discussion and review with the patient the dosage can be reduced and gradually withdrawn if deemed appropriate (see next page).
- For more information about cautions/contraindications of neuropathic pain treatment, please refer to the medication's summary of product characteristics (SPC).

Treatment withdrawal regimes

Drug name	Recommendation strategy for withdrawal
Amitriptyline/Nortriptyline	Reduce daily dose by 10mg each week
Gabapentin (total daily dose > 900mg)	Reduce total daily dose by 300mg every 4 days
Gabapentin (total daily dose ≤ 900mg)	Reduce total daily dose by 100mg every 4 days
Duloxetine	Reduce dose by 30mg every 3-4 days, then stop.
Pregabalin	Reduce total daily dose by 50mg every week
Lidocaine plasters	See South East London Guide to Deprescribing Lidocaine 5% Plasters in Primary Care

Taper the withdrawal regimen to take account of dosage and discontinuation symptoms (see Appendix 2). If complete withdrawal of treatment is not successful, the patient should continue on the last dose in the reduction regimen at which pain was tolerable and they should be engaged in discussion about long term goals and non-pharmacological management. If the patient has remained pain-free for 8 weeks afterwards, dose reduction or withdrawal should be reattempted.

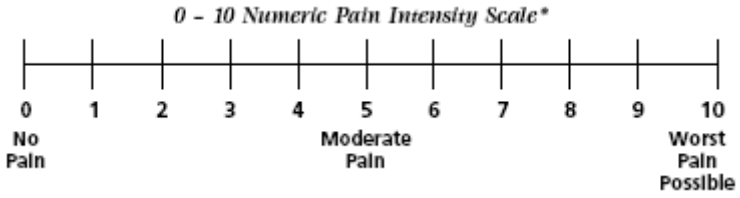
The following British Pain Society patient leaflets can support patients on specific neuropathic pain treatment options. It includes information on how their medication works, as well as a table to fill in regarding their individualised dosing schedule, in order to support titrating dose upwards/downwards.

- **Amitriptyline patient leaflet for pain**
- **Nortriptyline patient leaflet for pain**
- **Duloxetine patient leaflet for pain**
- **Pregabalin patient leaflet for pain**
- **Gabapentin patient leaflet for pain**

For more information and useful resources, which includes eLearning packages:

British Pain Society resources	https://www.britishpainsociety.org/about/articles-and-reports/
Faculty of Pain Medicine - eLearning for healthcare professionals	https://fpm.ac.uk/e-pain
ESCAPE-pain app – a useful tool for patients in managing their pain	https://escape-pain.org/escape-pain-app
Paintoolkit.org - designed for people who live with persistent pain and Healthcare teams who support them	https://www.paintoolkit.org/
Guys and St Thomas Medicines Information service	**Telephone:** 0207 188 8748 **Email**: medicinesinformation@gstt.nhs.uk

Appendix 1: Pain assessment – Numeric Rating Scale (NRS)



2 or more points/centimetres reduction indicates a significant benefit

Indicated for adults and children (>9 years old) in all patient care settings in which patients are able to use numbers to rate the intensity of their pain. This may also apply to children younger than 9 years where they have a firm understanding of numbers. The NRS consists of a straight horizontal line numbered at equal intervals from 0 to 10 with anchor words of "no pain", "moderate pain" and "worst pain". *(Breivik H et al. (2008) Assessment of pain. Br J Anaesth. 101 (1): 17-24)*

Appendix 2: Dose titration tables for neuropathic pain treatment

For up to date information about cautions/contraindications of neuropathic pain treatment, please refer to the medication's summary of product characteristics (SPC).

Amitriptyline or Nortriptyline

Up-titration schedule	Down titration schedule if ineffective
• Local pain consultants have advised maximum daily dose of **40mg** if patient derives benefit with limited side effects. • Take 1-2 hours before bed to reduce hangover effect and to promote sleep. • If patient experiences side effects then reduce dose by 10mg for 2 weeks before attempting an increase. • Avoid co-prescribing of tramadol as increased risk of central nervous system toxicity.	If less than 8 weeks, withdrawal effects unlikely. If greater than 8 weeks, wean off over 4 week period by reducing dose by 10mg each week.

	Week 1	Week 2	Week 3	Week 4
Night	10mg	20mg	30mg	40mg

Gabapentin

PHE-NHS England Pregabalin and Gabapentin Advice Dec 2014: Pregabalin or Gabapentin can lead to dependence and may be misused or diverted due to associated euphoric effect and should be avoided in patients with a known or suspected propensity to misuse, divert or become dependent.

Up-titration schedule

- Consider gradual titration in week 1 starting with 100mg at night on Day 1, slowly titrating to 100mg three times daily by Day 5. Dose should only be increased within the recommended increments (see below) where side effects are not a problem and treatment goals have not yet been achieved.
- Local pain consultants have advised that lower starting dose may improve tolerance, particularly for patients who have reported being sensitive to central nervous system depressant effects of other medication or in the elderly.
- Although the maximum daily dosage in BNF is 3600mg/day, local pain consultants have advised that most patients will achieve maximum therapeutic response at 2700mg/day.

Gabapentin initiation scheme				
	Week 1	**Week 2**	**Week 3**	**Week 4**
Morning	100mg	200mg	300mg	400mg
Midday	100mg	200mg	300mg	400mg
Night	100mg	200mg	300mg	400mg

Gabapentin dosage in Adults based on Renal Function	
Creatinine clearance (ml/min)	***Total Daily Dose in divided doses (mg/day)***
≥ 80	900-3600
50-79	600-1800
30-49	300-900
15-29	150-600mg (150mg = 300mg on alternate days)
<15	150-300mg (150mg = 300mg on alternate days)

Down titration schedule if ineffective

1) Where the total daily dose is greater than 900mg daily, this should be stepped down by 300mg every 4 days, unless observations of emergent symptoms are required, in which case more gradual dose tapering is needed, as seen in table below.

	Week 1	**Week 2**	**Week 3**
Morning	300mg	300mg	
Midday	300mg		
Night	300mg	300mg	300mg

2) Where the total daily dose is less than 900mg daily, this should be stepped down by 100mg every 4 days.

Pregabalin

PHE-NHS England Pregabalin and Gabapentin Advice Dec 2014: Pregabalin or Gabapentin can lead to dependence and may be misused or diverted due to associated euphoric effect and should be avoided in patients with a known or suspected propensity to misuse, divert or become dependent.

Up-titration schedule

- Patient may start on differing daily doses *e.g. 25mg in the morning, 50mg at night* to improve tolerability.
- Although it is licensed to be given in two or three divided doses, **it is more cost effective to prescribe pregabalin TWICE DAILY, and also improves patient compliance.**
- When the patient is stabilised on long term treatment, they should be prescribed a single dose strength of pregabalin for use twice daily (after using up stock at home for titration doses).

	Week 1	Week 2	Week 3
Morning	50mg	75mg	150mg
Night	50mg	75mg	150mg

For older patients (>75 years) or those with renal impairment: Start on 25mg twice daily. If creatinine clearance <30ml/min, it may be appropriate to give this as a daily dose as per table below.

Dosage of Pregabalin in Adults based on Renal Function			
Creatinine clearance (ml/min)	**Total pregabalin daily dose**		**Dose regimen**
	Starting dose (mg/day)	***Maximum dose (mg/day)***	
≥ 60	150	600	BD or TDS
≥ 30 - < 60	75	300	BD or TDS
≥ 15 - < 30	25 – 50	150	OD or BD
< 15	25	75	OD

Down titration schedule if ineffective

- Reduce by 50-75mg per week.
- Suggested withdrawal schedule for a dose of 150mg twice a day:

	Week 1	Week 2	Week 3	Week 4	
Morning	150mg	75mg	50mg	25mg	Stop and review patient
Night	75mg	75mg	50mg	25mg	

Duloxetine

avoid if creatinine clearance < 30ml/min. Potential for increased serotonergic effects (see BNF) when duloxetine and tramadol are used together – use with caution.

Up-titration schedule

- SPC states that response to treatment should be seen within 2-4 weeks of therapy.
- Review ongoing need at 8 weeks, followed by every 3 months thereafter.
- Due to the large inter-individual variability in duloxetine plasma concentration, some patients will respond insufficiently to 60mg and may benefit from a higher dose.

	Week 1	Weeks 2 – 4 (dependent upon response to initial dose)
Night	30mg	60mg

Where higher doses are required, gradually increase up to an effective dose or the patient's maximum tolerated dose of no greater than 120mg per day (in two divided doses).

Down titration schedule if ineffective

- Discontinue if inadequate response at 8 weeks.
- Reduce dose by 30mg every 3-4 days, then stop.

Tramadol

Potential for increased serotonergic effects (see BNF) when duloxetine and tramadol are used together – use with caution.

Up-titration schedule

- Initially 50mg TWICE A DAY (50mg at night in the elderly) with increments of 50mg/day every 3 days dependent upon patient response, up to a maximum of 400mg/day.

Down titration schedule if ineffective

- If patient does not experience therapeutic benefit, reduce dose by 50mg every 3-4 days (this is not evidence based).

Appendix 3 - Example of care plan for patients being transferred back to general practice

This care plan template is an example of good practice for patients who have been started on neuropathic pain treatment by the pain service. Pain specialists should aim to provide a standardised level of information and details when transferring patients back to their GP. This includes explaining why the treatment has specifically been chosen for the patient, which aims to empower GPs in optimally managing patients on pharmacotherapy treatment for neuropathic pain.

{Insert Address Details}

Direct dial no. (for urgent queries): XXXXXXXXX
Departmental Fax: XXXXXXXX
Office: XXXXXXXX
Email: XXXXXXXXXXXXXXX

Date……..

Dear Dr. ***{GP name}***

Your patient has been started on neuropathic pain treatment as outlined in their individualised care plan below. They have been given a supply of this medication ***{insert drug name}*** for ***{X}*** days from the date of this letter, and I would be grateful if you could kindly arrange the prescription for this patient after this supply runs out.

Care Plan

Re: ***(Insert patient's name)*** **Hospital no:**……..

NHS no: …… **DOB:** ……..

Name of specialist: ……

Specific disease description (include pain scores):

……
……..
……

Medication details:

Drug name: …….. **Dose :……..**

Date of initiation: …….. **Length of treatment: ……**

Date of next treatment review : ……

Treatment aims/goals :

- To achieve 20-50% reduction in pain

{Include what this would look like for patient, based on their current pain experience}

- If pain is adequately controlled after 12 months, to consider gradually reducing dose
  {Include any other treatment aims/goals}

Dosing schedule for treatment: ***{Please insert relevant titration dose schedule for medication prescribed}***

Initiation scheme				
	Week 1	**Week 2**	**Week 3**	**Week 4**
Morning				
Midday				
Night				

Non-pharmacological treatment recommendations (where relevant):

{This including physiotherapy, and other psycho-social factors to consider}

……

……

……

The following monitoring should be undertaken by the GP:

{Outline whether the pain service would follow up patient at 8 week period, or if GP is expected to do this}

CRISIS PLAN

Signs/symptoms that require advice from or referral back to pain specialist

If the patient experiences any of these signs or symptoms whilst on therapy – they should report to their GP without delay:

Signs/symptoms the patient may experience whilst on therapy, but can be managed in primary care:

References:

1. **NICE Clinical Guideline 173 :** Neuropathic pain in adults: pharmacological management in non-specialist settings https://www.nice.org.uk/guidance/cg173 *November 2013*
2. **Gloucestershire CCG pain guidelines:** http://www.gloshospitals.nhs.uk/en/Wards-and-Departments/Departments/Pain-Management/Different-Pains/Nerve-Pain/Draft-Neuropathic-pathway/ *June 2016*
3. **PrescQIPP Bulletin 119** : Pregabalin in neuropathic pain https://www.prescqipp.info/pregabalin-in-neuropathic-pain/category/80-pregabalin-in-neuropathic-pain *January 2016*
4. **Mid Essex CCG:** Neuropathic pain guidelines *June 2016*
5. **Drug Tariff:** *July 2017*
6. **British National Formulary:** BNF British National Formulary - NICE
7. Electronic Medicines Compendium: Cymbalta 30mg hard gastro-resistant capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)