SEL Pharmacological Management of Neuropathic Pain in Adults in primary care

All patients should be reviewed at 8 weeks after treatment has been started to establish ongoing need to continue therapy.

1st line

***AMITRIPTYLINE**

Counsel patient that it will take **6-8 weeks** to achieve a therapeutic response. **Contraindications to therapy** include patients with:
a recent myocardial infarction, arrhythmia, on other antidepressants, a history of prostatism, or narrow angle glaucoma.

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

Amitriptyline dosing Instructions

- Initiate dose at 10mg/night and **gradually uptitrate by 10mg in weekly increments** until either the patient experiences a therapeutic response or cannot tolerate dose.
- Local pain consultants have advised up to 40mg maximum dose may be used if patient derives benefit with limited side effects.
- If patient experiences side effects then reduce dose by 10mg for 2 weeks before attempting an increase.
- 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 be considered, using the same dose instructions as amitriptyline.

2nd line

****GABAPENTIN**

Start dose at 100mg/day*** and based upon patient's response, gradually titrate up to a maximum of 3600mg/day in 3 divided doses. Stop when patient reaches pain relief goals, or experiences intolerable side-effects (most will achieve this by 2700mg/day). Patients should be counselled that they may not feel pain relief straightaway, as they are building tolerability to the medication.

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.

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

3rd line

****PREGABALIN**

Start dose at 50mg TWICE DAILY (25mg for elderly or 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 - *Consider for patients **with painful diabetic neuropathy.***

Start dose at 30mg daily and based upon patient's response, gradually titrate upwards to 60mg daily. 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.

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.

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

4th line – combination therapy

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 APC position statement).*

Localised neuropathic pain

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

CAPSAICIN **0.075% CREAM** under the supervision of a hospital specialist. A pea sized amount should be applied up to 4 times daily for 6-8 weeks.

Treatment only to be initiated in specialist care/pain clinic

- Opioids *e.g. Morphine,Oxycodone,Tapentadol*
- Topical capsaicin 179 mg (8%) patch
- Nabilone **(RED listed – hospital only)**
- Ketamine oral solution **(RED listed – hospital only)**
- Other antiepileptics *e.g. Lamotrigine, Topiramate,*
- Other antidepressants e.g. Venlafaxine

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

- **LIDOCAINE 5% (700mg) PLASTERS** (AMBER 2) for treatment of ***post-herpetic neuralgia*** and ****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 APC position statement.

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 1.2g daily. If carbamazepine is inappropriate, ineffective, or not tolerated, seek specialist advice. Do ***not*** offer any other drug treatment 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

*** Consider gradual titration in week 1 starting with 100mg at night on Day 1, slowly titrating to 100mg three times daily by Day 5.

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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).
- Pain assessment scales, including the 10-point Numeric Rating Scale (**NRS**) or Visual Analogue Scale **(VAS**) 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. This can be done 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** is the preferred ACB scale to use, as its development is more robust and evidence based compared to other ACB scales. This is available as a web-based app at www.medichec.com, where prescribers can:
  - Type the name of the medications into the search bar to reveal its AEC score
  - Add each medication to a list to calculate the total score
  - Email a summary or export as a PDF
- The goal of neuropathic pain treatment is to support initial symptomatic relief for people such that they are sufficiently able to engage in non-pharmacological treatment such as light exercise, physiotherapy, relaxation techniques and rehabilitation.
- 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.
- Trial all treatments 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
  - Daily activities and participation (such as ability to work and drive)
  - Mood (in particular, possible depression and/or anxiety)
  - Quality of sleep
  - Overall improvement as reported by the patient.
- **Referral to specialist pain service** should be considered at any stage if:
  - Patient has severe pain
  - Pain significantly limits their daily activity and participation
  - 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)*
- Please refer to Appendix 3 to see an 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 daily dose by 30mg each week, following a week of 30mg daily, take 30mg on alternate days for 1 week and then stop
Pregabalin	Reduce total daily dose by 50mg every week

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.

You may wish to use the British Pain Society patient leaflets below to 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**

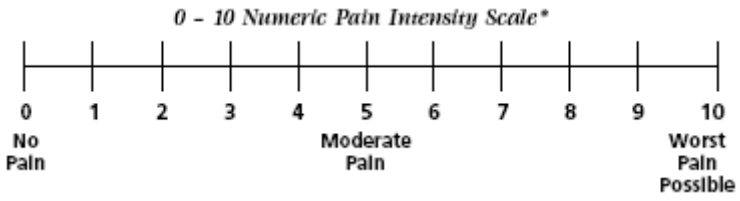
For more information and useful resources, which includes eLearning packages:

- British Pain Society resources
  https://www.britishpainsociety.org/about/articles-and-reports/
- Faculty of Pain Medicine - eLearning for healthcare professionals
  http://www.rcoa.ac.uk/faculty-of-pain-medicine/e-pain
- ESCAPE-pain app – a useful tool for patients in managing their pain
  http://www.escape-pain.org/about-escape/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 scales

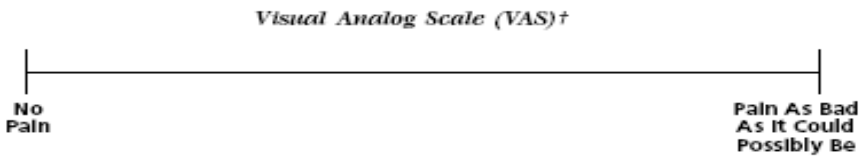
2 or more points/centimetres reduction indicates a significant benefit.

1. Numeric Rating Scale (NRS)



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. 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)

2. Visual Analogue Scale (VAS)



The left endpoint (0) corresponds to “no pain” and the right endpoint (100) is defined as “pain as intense as it can be.” †A 10-cm baseline is recommended for VAS scales.

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

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.
- Although BNF states maximum dose for diabetic neuropathy is 120mg (in divided doses) trials showed no benefit to 120mg dose over 60mg (NNT for 50% pain reduction 5.7 and 5.8 respectively).
- Avoid if creatinine clearance < 30ml/min.

	Week 1	Weeks 2 – 4*
Night	30mg	60mg

****dependent upon response to initial dose***

Down titration schedule if ineffective

- Discontinue if inadequate response at 8 weeks.
- Reduce daily dose by 30mg each week, following a week of 30mg daily, take 30mg on alternate days for 1 week and 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 73:** *March 2017*