This policy statement is approved by Halton, Knowsley, Liverpool, Southport and Formby, South Sefton, St Helens, Warrington, Wirral and West Lancashire CCGs

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NEUROPATHIC PAIN GUIDELINES
Pharmacological management in non-specialist settings
in ADULTS

IMPORTANT: Assess person & confirm diagnosis of neuropathic pain using, if required, validated tools or questionnaires[1] Ensure **accurate** diagnosis of neuropathic pain and appropriate management of underlying condition[1,2]

This guideline is for use in primary care for initial management, not in specialist pain service settings.

NEUROPATHIC PAIN
(except trigeminal neuralgia)

AMITRIPTYLINE*

OR

GABAPENTIN[A]

If contraindicated, ineffective at maximum tolerated dose or unable to tolerate adverse effects switch to:

PREGABALIN[B] OR DULOXETINE[C]

If contraindicated, ineffective at maximum tolerated dose or unable to tolerate adverse effects switch to: alternative agent

PREGABALIN[B] OR DULOXETINE[C]

AFTER STARTING OR CHANGING TREATMENT PERFORM AN EARLY CLINICAL REVIEW OF DOSAGE TITRATION, TOLERABILITY AND ADVERSE EFFECTS TO ASSESS SUITABILITY OF CHOSEN TREATMENT.

REVIEW REGULARLY (EVERY 2-6 WEEKS) TO MONITOR EFFECTIVENESS OF TREATMENT, INCLUDING:

- PAIN REDUCTION
- ADVERSE EFFECTS
- DAILY ACTIVITIES AND PARTICIPATION (E.G. WORK AND DRIVING)
- MOOD (IN PARTICULAR POSSIBLE DEPRESSION &/OR ANXIETY)
- QUALITY OF SLEEP
- OVERALL IMPROVEMENT

CONSIDER CAPSAICIN CREAM[D] FOR PEOPLE WITH LOCALISED NEUROPATHIC PAIN WHO WISH TO AVOID, OR WHO CANNOT TOLERATE ORAL TREATMENT. OR AS ADJUNCT THERAPY. TAKE NOTE THAT IN SOME INSTANCES THIS IS OFF LABEL.

TRAMADOL SHOULD ONLY BE CONSIDERED IF ACUTE RESCUE ANALGESIA IS NEEDED (NOT FOR LONG TERM USE)

TRIGEMINAL NEURALGIA

CARBAMAZEPINE

If initial treatment with carbamazepine is not effective, not tolerated or contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.

Satisfactory pain reduction

Continue treatment—consider gradually reducing over time if improvement sustained [2]

LIDOCAINE PATCHES MAY ONLY BE COMMENCED BY A PAIN OR PALLIATIVE CARE SPECIALIST IN LINE WITH SPECIFIED CRITERIA, SEE LINK (MAY BE COMMENCED IN PRIMARY CARE FOR POST HERPETIC NEURALGIA ONLY)

Consider referring person to specialist pain clinic at any stage, including initial presentation and at the regular reviews if:

- they have severe pain **or**
- pain significantly limits their daily activities and participation **or**
- their underlying health condition has deteriorated[2]

DOSAGE TITRATION
The dose should be optimised for the recommended duration - see page 2 - (unless patient is experiencing adverse effects, or unable to tolerate drug) before considering changing to alternative.[2]

* **NORTRIPTYLINE** may be used if amitriptyline is not tolerated. Nortriptyline is significantly more expensive.

When agreeing a treatment plan with the person, take into account their concerns and expectations, and discuss the importance of dosage titration and the titration process, providing the person with individualised information and advice.

A. Licensed for peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.
B. Licensed for peripheral and central neuropathic pain.
C. Licensed for diabetic peripheral neuropathic pain. Use caution if co-prescribed an SSRI. Do not use duloxetine with fluvoxamine.
D. Licensed for post-herpetic neuralgia after open skin lesions have healed and painful diabetic peripheral polyneuropathy[1]

THESE RECOMMENDATIONS TAKE INTO ACCOUNT NICE CLINICAL GUIDELINE 173. NEUROPATHIC PAIN - THE PHARMACOLOGICAL MANAGEMENT OF NEUROPATHIC PAIN IN ADULTS IN NON-SPECIALIST SETTINGS. NOVEMBER 2013 (updated April 2018). [1]

IMPORTANT POINTS

- Amitriptyline is contraindicated in **arrhythmias**, **severe liver disease,** recent **MI** & manic phase of bipolar disorder. Cautioned in **elderly** (adverse effects more common), CVD, history of seizures, glaucoma, or urinary retention (see SPC for further cautions, etc).[2,3]
- For pregabalin and gabapentin weight gain is a common undesirable effect and therefore this must be taken into consideration when selecting therapy in certain people e.g. patients with diabetes (see SPC for further cautions, etc). [2,3]
- See MHRA safety warning for Duloxetine; cases of **suicidal ideation** and suicidal behaviour [4]
- The combination of tramadol with amitriptyline or duloxetine is associated with a risk of serotonin syndrome (features of this include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus). [5]
- A specialist pain clinic **and/or** a condition specific service is a specialist service providing treatment for the underlying health condition that is causing neuropathic pain, e.g. neurology, diabetology and oncology. [2]
- There are concerns around the abuse potential of gabapentin and pregabalin.

Box A: Drug dosages and information (Do *not* prescribe more than one neuropathic pain drug at the same time.)

Drug	Price*	Starting Dose	Titration	Maximum Dose	Renal Impairment	Duration of adequate trial
Amitriptyline	£[6]	10-25mg/day (at bed time) [7]	Increase gradually, if necessary, by 10mg at night every 3-7 days, as tolerated, to 75 mg/day [7]	**75 mg/day** [7] Consider consultation with specialist pain service for higher doses.	No dose reduction recommended.[3]	6-8 weeks with at least 2 weeks at maximum tolerated dose. (Do not stop abruptly, reduce gradually over 4 weeks (6 months if been taking long term)).
Duloxetine	££[6]	60mg/day [3,7,8]	60mg daily is usual maintenance dose, some patients may benefit further from increase to 60mg twice daily	**60mg twice/ day** [3,7] Consider consultation with specialist pain service for higher doses.	Avoid if creatinine clearance < 30ml/ min[3,7]	8 weeks with at least 4 weeks at maximum dose. (Do not stop abruptly, decrease dose gradually over 1 to 2 weeks).
Gabapentin	££[6]	See Supplementary Sheet— Recommended Dose Titrations	See Supplementary Sheet— Recommended Dose Titrations	**1200mg three times/day** [7]	Dose reduction dependent on degree of renal impairment— see supplementary sheet	3-8 weeks for titration plus 2 weeks at maximum dosage. (Do not stop abruptly, discontinue gradually over minimum 1 week).
Pregabalin	££[6]	See Supplementary Sheet— Recommended Dose Titrations	See Supplementary Sheet— Recommended Dose Titrations	**300mg twice/ day** [7]	Dose reduction dependent on degree of renal impairment— see supplementary sheet	4 weeks (Do not stop abruptly, discontinue gradually over minimum 1 week)
Carbamazepine	££[6]	100mg 1-2 times/day	Increase gradually according to response: usual dose 200mg 3-4 times daily (some may require higher initial dose)	Up to **1.6 g daily** in some people [7] **Prescribe as generic in neuropathic pain**	Dose as in normal renal function	
Tramadol	££[6]	50mg not more often than every 4 hrs	Increase to 100mg four times a day (not more often than every 4 hours) if necessary as tolerated.	**400 mg/day** [7]	Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs. Caution (avoid for oral drops) in severe impairment.[7]	Acute use only
Capsaicin 0.075% cream	££[6]	Three to four times a day [3,7]	A pea sized amount should be applied to the affected area not more often than every 4 hours. [3.7]	Four times a day [3,7]	No information	8 weeks then review [3]

*Price/28 days: £ = £0-3.00, ££ = £3.01-21, £££=£21.01-60, ££££=£>60.00

REFERENCES

1. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening 5 questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-20.
2. NICE Clinical Guideline 173. Neuropathic pain - The pharmacological management of neuropathic pain in adults in non-specialist settings. November 2013 (updated April 2018)(accessed 30th July 2018)
3. Summary of Product Characteristics. www.medicines.org.uk/emc/ (accessed 30th July 2018).
4. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON079177 (accessed 28th July 2018
5. Stockleys Drug Interactions https://www.medicinescomplete.com/#/browse/stockley (accessed 30th July 2018)
6. Dictionary of Medicines and Devices browser. http://dmd.medicines.org.uk/ (accessed 30th July 2018)
7. Joint Formulary Committee. *British National Formulary.* [BNF online]. London: BMJ Group and Pharmaceutical Press; 20168[updated 2018 Available from: http://www.medicinescomplete.com/#/browse/bnf] (accessed 30th July 2018)

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication. If there is good evidence to support that use, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's 'Good practice in prescribing and managing medicines and devices' (2013).

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SUPPLEMENTARY SHEET – RECOMMENDED DOSE TITRATIONS AND DOSE REDUCTIONS IN RENAL IMPAIRMENT FOR GABAPENTIN AND PREGABALIN

These dose titrations are based on local specialist experience in Pan-Mersey and are possible options. Although they don't reflect the dose titrations in the Summary of Product Characteristics and British National Formulary they are often more suitable and better tolerated.

DOSE TITRATION FOR THE INITIATION OF GABAPENTIN

Dosing chart

Day 1-3	Day 4-6	Day 7-13	Day 14-21	Day 22
100mg once a day	100mg twice a day	100mg three times a day	200mg three times a day	300mg three times a day.

Please note: slower titration may be appropriate for some patients e.g elderly

Day 22 onwards
Dose may be increased by 300 mg/day, if necessary, ideally at weekly intervals, up to a maximum of 3600 mg per day.

Please note these increments are only required if patient has not achieved adequate pain relief - the patient should be reviewed regularly (every 2 -6 weeks - see management flow chart).

DOSE RECOMENDATIONS IN RENAL IMPAIRMENT FOR GABAPENTIN

Creatinine clearance (mL/min)	**Total daily dose (mg/day) (administered in three divided doses)**
≥ 80	900-3600
50 – 79	600-1800
30 – 49	300-900
15 – 29	150 (as 300mg on alternate days) - 600
<15*	150 (as 300mg on alternate days) - 300
* daily dose should be reduced in proportion to creatinine clearance	
For anuric patients undergoing haemodialysis who have never received gabapentin; give loading dose 300 to 400 mg, then 200 to 300 mg following each 4 hours of haemodialysis. (No treatment on dialysis-free days)	
For renally impaired patients undergoing haemodialysis dose as in table above. In addition to maintenance dose, give an additional 200 to 300 mg dose following each 4 hour haemodialysis treatment.	

DOSE TITRATION FOR THE INITIATION OF PREGABALIN

Please note these increments are only required if patient has not achieved adequate pain relief - the patient should be reviewed regularly (every 2 to 6 weeks - see management flow chart)

Option One	Day 1-7	Day 8-14	Day 15
	25mg twice daily	50mg twice daily	As per option 2 from day 1
Option Two	Day 1-7	Day 8-14	Day 15
	75mg twice daily	150mg twice daily	300mg twice daily

Please note: slower titration may be appropriate for some patients e.g. elderly

DOSE RECOMMENDATION IN RENAL IMPAIRMENT FOR PREGABALIN

Creatinine clearance (mL/min)	**Total pregabalin daily dose (two divided doses)**		**Dose regimen**
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	Two divided doses
≥ 30 - < 60	75	300	Two divided doses
≥ 15- < 30	25 – 50	150	Once daily or two divided doses
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single (additional) dose

1. Summaries of product characteristics www.medicines.org.uk/emc/ (accessed 31st July 2018).
2. Joint Formulary Committee. *British National Formulary.* [BNF online]. London: BMJ Group and Pharmaceutical Press; 20168 [updated 2018 Available from: http://www.medicinescomplete.com/#/browse/bnf((accessed 31st July 2018).