Lancashire & South Cumbria Medicines Management Group

NHS Midlands and Lancashire Commissioning Support Unit

New Medicine Recommendation

Nortriptyline tablets (10mg and 25mg) for Chronic Neuropathic Pain (3rd line)

Recommendation:
GREEN (RESTRICTED)
Appropriate for initiation and ongoing prescribing in both primary and secondary care provided:
Additional criteria specific to the medicine or device are met, or
The medicine or device is used following the failure of other therapies as defined by the relevant LSCMMG pathway.
Generally, little or no routine drug monitoring is required.

NB. This New Medicines Recommendation is only applicable to the 10mg and 25mg tablet forms of Nortriptyline – the 50mg tablet is not to be prescribed (the 50mg tablet is not a Category M medicine).

Nortriptyline is only to be used as 3rd line treatment, for chronic neuropathic pain, in patients where ineffectiveness of or intolerance to amitriptyline and gabapentin has been demonstrated.

Summary of supporting evidence:

- The effect of tricyclic antidepressants in neuropathic pain (NP) in man has been demonstrated in numerous randomised, controlled trials
- Tricyclic antidepressants will relieve one in every 2–3 patients with peripheral neuropathic pain
- There is evidence that nortriptyline is effective in treating neuropathic pain, but there is still debate over when it should be used.
- The European Federation of Neurological Societies (EFNS) Guidelines recommend tricyclic antidepressants, including Nortriptyline, as first line treatment for painful polyneuropathy (PPN) (which is a common NP condition) and for post herpetic neuralgia
- The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain Guidelines, recommend tricyclic antidepressants (TCAs) as first line treatment, in particular nortriptyline due to its better adverse event profile.
- The results of one review do not support the use of nortriptyline as a first line treatment. However, there appears to be general agreement that tricyclic antidepressants have approximately equivalent efficacy, and if treatment of an individual fails with one it is worthwhile trying another i.e. second / third line.
- Anticholinergic adverse effects from TCAs are common, however, these effects can be reduced by starting with low dosages administered at bedtime and with slow titration to higher dosages and also by using a secondary amine TCA such as nortriptyline

Details of Review

Name of medicine (generic & brand name)**:** Nortriptyline tablets
Strength(s) and form(s): 10mg and 25mg tablets only
Dose and administration:

For neuropathic pain (unlicensed) – initially 10mg once daily, to be taken at night. Increased if necessary to 75mg daily. Dose to be increased gradually; higher doses to be given under specialist supervision.[i]

BNF therapeutic class / mode of action
Nervous system : Tricyclic antidepressant, it is the principle active metabolite of amitriptyline.

Licensed indication(s):
Nortriptyline is indicated for the relief of symptoms of depression. It may also be used for the treatment of some cases of nocturnal enuresis.

Proposed use (if different from, or in addition to, licensed indication above):
Neuropathic pain (3rd line)

Course and cost:[ii]
Nortriptyline 10mg tablets = £7.64 / 100 tablets
Nortriptyline 25mg tablets = £8.78 / 100 tablets
At minimum dose of 10mg daily, monthly cost / patient = 28 x £0.08 = £2.24
At maximum dose of 75mg daily, monthly cost / patient = 28 x £0.26 = £7.28 (3x 25mg tablets)

Current standard of care/comparator therapies:
Nortriptyline is proposed to be used third line after amitriptyline and gabapentin.
The current 3rd line treatment recommended in the LSCMMG Neuropathic Pain Guidance (after amitriptyline and gabapentin) is either pregabalin or duloxetine (if diabetic neuropathy).
Amitriptyline is not licensed for neuropathic pain
Pregabalin - Start at 75mg twice daily, titrate upwards until efficacy achieved or not tolerated. Reduced doses required in renal impairment. The rate of increase should be guided by patient & tolerability.
Usual Therapeutic Dose Range: 150-600mg daily in divided doses
Drug Tariff Price[ii]
Pregabalin 75mg capsules = £2.67 / 56 capsules
Pregabalin 150mg capsules = £3.74 / 56 capsules
Pregabalin 300mg capsules = £5.34 / 56 capsules
At recommended starting dose of 75mg twice daily, the monthly cost / patient = £2.67
At maximum recommended dose of 300mg twice daily, the monthly cost / patient = £5.34
Duloxetine - Start at 60mg daily (a 30mg starting dose may be appropriate for some patients). Increase to 60mg twice daily after 1 week if needed.
Drug Tariff Price[ii]
Duloxetine 60mg gastro-resistant capsules = £2.34 / 28 capsules
At recommended starting dose of 60mg daily, the monthly cost / patient =£2.34
At maximum recommended dose of 60mg twice daily, the monthly cost / patient = £4.68

Relevant NICE guidance:
Neuropathic pain in adults: pharmacological management in non-specialist settings, Clinical guideline [CG173].[iii] The guidance states the following:

> ***All neuropathic pain (except trigeminal neuralgia)***
> 1.1.8 Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)
> 1.1.9 If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.
> 1.1.10 Consider tramadol only if acute rescue therapy is needed.
> 1.1.11 Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Nortriptyline is therefore not a NICE recommended drug however the drug is also not listed in the 'Treatments that should not be used' section of the guideline.

Background and context

A request was received from the Lancashire Care Community Pain Team for Nortriptyline to be considered as a 3rd line option for treating chronic neuropathic pain.
The request was made as drug choices are limited and the applicant felt that nortriptyline is useful in specific circumstances.
Nortriptyline is approved for use in the Pan Mersey region, this impacts the specialist pain service as some clinicians cover both Preston and Southport.

Summary of evidence

Summary of efficacy data in proposed use:

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010, 17: 1113–1123[iv]

The European Federation of Neurological Societies (EFNS) Guidelines feature a table assigning classification of evidence for drug treatments in commonly studied neuropathic pain conditions and recommendations for use. Tricyclic antidepressants, including Nortriptyline, are shown as having level A rating for efficacy in diabetic neuropathic pain/ post herpetic neuralgia and level B rating for efficacy in spinal cord injury / central post stroke pain / multi-aetiology neuropathic pain. The guidelines recommend the use of tricyclic antidepressants as first line treatment for painful polyneuropathy (PPN) (which is a common NP condition) and for post herpetic neuralgia.

Antidepressants in the Treatment of Neuropathic Pain 2005[v]

This review details the pharmacology of antidepressants in relation to neuropathic pain mechanisms and presents the evidence for the use of antidepressants and their efficacy in different neuropathic pain conditions.

Tricyclic antidepressants may relieve neuropathic pain by their unique ability to inhibit presynaptic reuptake of serotonin and noradrenaline, other mechanisms such as N-methyl-D-aspartate receptor and ion channel blockade probably also play a role in their pain-relieving effect. The effect of tricyclic antidepressants in neuropathic pain in man has been demonstrated in numerous randomised, controlled trials, and a few trials have shown that serotonin noradrenaline and selective serotonin reuptake inhibitor antidepressants also relieve neuropathic pain although with lower efficacy. Tricyclic antidepressants will relieve one in every 2–3 patients with peripheral neuropathic pain, serotonin noradrenaline reuptake inhibitors one in every 4–5 and selective serotonin reuptake inhibitors one in every 7 patients. Thus, based on efficacy measures such as numbers needed to treat, tricyclic antidepressants tend to work better than the anticonvulsant gabapentin and treatment options such as tramadol and oxycodone, whereas the serotonin noradrenaline reuptake inhibitor venlafaxine appears to be equally effective with these drugs and selective serotonin reuptake inhibitors apparently have lower efficacy.

The review also states that demethylation of the side chain seems to be important in reducing side effects, as seen with amitriptyline and its demethylated metabolite nortriptyline.

Nortriptyline for neuropathic pain in adults (2015)[vi]

This Cochrane review included six studies treating 310 participants with various neuropathic pain conditions. Five studies used a cross-over design, and one used a parallel-group design; 272 participants were randomised to treatment with nortriptyline, 145 to placebo, 94 to gabapentin, 56 to gabapentin plus nortriptyline, 55 to morphine, 55 to morphine plus nortriptyline, 39 to clomipramine, and 33 to amitriptyline. Treatment periods lasted from three to eight weeks. Only one study reported the primary outcome of people with at least 50% reduction in pain,[vii] but three reported outcomes considered equivalent to another relevant primary outcome of Patient Global Impression of Change[1] being much or very much improved.

Data could not be pooled, but third tier evidence in individual studies indicated similar efficacy to other active interventions (gabapentin, morphine, clomipramine, and amitriptyline), and to placebo in the conditions studied (very low quality evidence). All studies had one or more sources of potential major bias, this was mainly from small study size and short study duration. No study provided first or second tier evidence for any outcome.

The results of this review do not support the use of nortriptyline as a first line treatment. However, there appears to be general agreement that tricyclic antidepressants have approximately equivalent efficacy, and if treatment of an individual fails with one it is worthwhile trying another.

Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update (2010)[viii]

[1] This scale evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status

These guidelines were produced by The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain.
The NeuPSIG guidelines recommend medications as:

- first line treatment if efficacy in NP has been established in multiple RCTs (Oxford Centre for Evidence-based Medicine grade A recommendation), and these results are consistent with the authors' clinical experience;
- second-line if efficacy in NP has been established in multiple RCTs (grade A recommendation), but there were reservations about the use of the medication relative to the first-line medications based on the authors' clinical experience; and
- third-line if only one RCT has shown efficacy in NP or if the results of 2 or more RCTs were inconsistent (grade B recommendation), but the authors thought that in selected circumstances the medication may be a reasonable treatment option.

Because many patients treated with a single efficacious medication do not obtain satisfactory pain relief, the guidelines emphasise that patients may benefit from use of combinations of efficacious NP medications.
First-line medicine recommendations are: antidepressants with both Norepinephrine and Serotonin Reuptake Inhibition. A large number of placebo-controlled RCTs have found tricyclic antidepressants (TCAs) to be efficacious for several different types of NP. However, anticholinergic adverse effects are common and include dry mouth, orthostatic hypotension, constipation, and urinary retention. These effects can be reduced by starting with low dosages administered at bedtime and with slow titration to higher dosages and also by using a secondary amine TCA (**nortriptyline** or desipramine).
A qualitative systematic review of head-to-head randomized controlled trials of oral analgesics in neuropathic pain 2010[ix]
A systematic review of RCTs involving NP patients was performed, of which head-to-head comparative trials were selected. Reference lists from published systematic reviews were searched. These studies were rated according to the Jadad[2] scale for quality.
Twenty-seven such trials were identified. Seventeen were comparisons of different analgesics, and 10 were of different drugs within an analgesic class. Important information was obtained about the relative efficacy and safety of drugs in different categories and within a category. Some significant differences between active treatments were reported. Trial inadequacies were identified.
In summary the review found that with regard to antidepressant comparisons, the TCAs amitriptyline, nortriptyline, desipramine and imipramine do not appear to differ in analgesic efficacy. There is some evidence that the more noradrenergic, weaker serotonergic TCAs nortriptyline and desipramine are equal to or more effective than the dual noradrenergic/ serotonergic agent amitriptyline.
The review concludes that more and improved head-to-head RCTs are needed to inform clinical choices.
Algorithm for neuropathic pain treatment: An evidence based proposal[x]
This clinical paper utilised a literature review to produce an algorithm for the treatment of neuropathic pain. Criteria such as clinical trial efficacy, persistence of effect, adverse events, effect on quality of life and cost were taken into account when formulating the algorithm. Step 2 of the algorithm, which is when the first drug therapy is introduced is as follows:

Initiate therapy of the disease causing NP, if applicable
Initiate symptom treatment with one or more of the following:

- A secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel a2-d ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies

Evaluate patient for non-pharmacologic treatments, and initiate if appropriate

[2] The Jadad scale, is a procedure to independently assess the methodological quality of a clinical trial. Jadad et al. published a three-point questionnaire that formed the basis for a Jadad score.

Other efficacy data:

NICE Clinical guideline [CG173] Neuropathic pain in adults: pharmacological management in non-specialist settings[xi]

Nortriptyline was included in the full guideline evidence review which stated that there is insufficient evidence to determine whether nortriptyline is better or worse than its comparators. However, overall with regard to pain the majority of the results from the analyses showed that nortriptyline consistently reduced pain compared with placebo. It was also concluded that nortriptyline's mean cost-per-QALY appeared to represent poor value for money compared with gabapentin and amitriptyline. However, the GDG was mindful that estimates of nortriptyline's effectiveness are highly uncertain. Because of this, it was not possible to exclude the possibility that it may be an extremely effective option and, as a direct consequence, probabilistic analysis showed that there is a greater than 15% probability that nortriptyline provides the most cost-effective option when QALYs are valued at between £20,000 and £30,000 (which, in the context of pervasive uncertainty, compares well with other options).

The GDG also noted evidence that nortriptyline may be somewhat better tolerated than amitriptyline, with lower incidence of events in 7 of 10 safety network meta-analyses in which there was evidence for both drugs, with significant benefits estimated for fatigue and weight gain. The GDG was aware that this benefit may not have been fully captured in the health economic model. The uncertainty inherent in the estimate of nortriptyline's effectiveness, coupled with its comparatively high acquisition cost, made it difficult to exclude the possibility that it is a poor choice of treatment: it was no more cost effective than placebo in 43% of model iterations.

Taking these considerations into account, the GDG felt it was not possible to make a positive recommendation in support of nortriptyline, either as an initial treatment option or at a later stage in the treatment pathway. **However, it was also not convinced that sufficient evidence had been adduced to enable them to make a recommendation suggesting that nortriptyline should not be used.**

Therefore, the GDG agreed that this was a treatment for which it would not be helpful to make an explicit recommendation.

It should be noted that:

- The health economic model used by NICE was based on a daily dosage of 5 x 25mg Nortriptyline tablets which is higher than the recommended maximum dosage.
- The Drug Tariff price for Nortriptyline was significantly higher at that time of the NICE review
- NICE CG173 is for the pharmacological management of neuropathic pain in adults in **non**-specialist settings
- Because of the risk of abuse and dependence, pregabalin and gabapentin are controlled under the Misuse of Drugs Act 1971 as Class C substances and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3 (as of 1st April 2019).

Summary of safety data:

Undesirable effects[xii]

The following list of adverse events are from an SPC for nortriptyline.

Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000) not known (cannot be estimated from the available data).

System organ class	Frequency	Preferred Term
Blood and lymphatic system disorders	Rare	Bone marrow depression, agranulocytosis, leucopenia, eosi thrombocytopenia.
Endocrine disorders	Not Known	Syndrome of inappropriate secretion of antidiuretic hormo (SIADH)
Metabolism and nutrition disorders	Rare	Decreased appetite.
	Not Known	changes of blood sugar levels
Psychiatric disorders	Very common	aggression
	Common	Confusional state, libido decreased, agitation
	Uncommon	Hypomania, mania, anxiety, insomnia, nightmare.
	Rare	Delirium (in elderly patients), hallucination (in schizophreni patients).
	Not Known	*Suicidal ideation and suicidal behaviour, paranoia
Nervous system disorders	Very common	Tremor, dizziness, headache.

	Common	Disturbance in attention, dysgeusia, paresthesia, ataxia.	
	Uncommon	Convulsion.	
	Rare	akathisia, dyskinesia	
	Not Known	Extrapyramidal disorder	
Eye disorders	Very common	Accommodation disorder.	
	Common	Mydriasis.	
	Very rare	Acute glaucoma	
Ear and labyrinth disorders	Uncommon	Tinnitus.	
Cardiac disorders	Very common	Palpitations, tachycardia	
	Common	Atrioventricular block, bundle branch block.	
	Uncommon	Collapse conditions, worsening of cardiac failure	
	Rare	Arrhythmia.	
	Very rare	Cardiomyopathies, torsades de pointes	
	Not Known	hypersensitivity myocarditis	
Vascular disorders	Common	Orthostatic hypotension.	
	Uncommon	Hypertension	
	Not known	Hyperthermia	
Respiratory, thoracic, and mediastinal disorders	Very common	Congested nose.	
	Very rare	Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome)	
Gastrointestinal disorders	Very common	Dry mouth, constipation, nausea.	
	Uncommon	Diarrhoea, vomiting, tongue oedema.	
	Rare	Salivary gland enlargement, ileus paralytic.	
Hepatobiliary disorders	Uncommon	Hepatic impairment (e.g. cholestatic liver disease).	
	Rare	Jaundice.	
	Not Known	Hepatitis	
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis.	
	Uncommon	Rash, urticaria, face oedema.	
	Rare	Alopecia, photosensitivity reaction.	
Renal and urinary disorders	Uncommon	Urinary retention.	
	Common	Micturition disorders	
Reproductive system and breast disorders	Common	Erectile dysfunction.	
	Uncommon	Galactorrhoea.	
	Rare	Gynaecomastia	
General disorders and administration site conditions	Common	Fatigue, feeling thirst	
	Rare	Pyrexia.	
Investigations	Very common	Weight increase	
	Common	Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia.	
	Uncommon	Intraocular pressure increased.	
	Rare	Weight decreased. Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased.	

*Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early after treatment discontinuation

Adverse Effects of Antidepressants for Chronic Pain: A Systematic Review and Meta-analysis (2017)[xiii]

This was a systematic literature research and meta-analyses were performed regarding side effects and safety of different antidepressants in the treatment of chronic pain. Out of 1,975 screened articles, 33 papers published between 1995 and 2015 were included in the review; 23 studies were included in the meta-analyses. A higher risk for adverse effects compared to placebo was observed in all antidepressants included in the analyses, except nortriptyline.

Adverse effects with strong evidence for nortriptyline were: constipation (RR 1.84; 95%-CI [0.90; 3.74]), drowsiness (RR 3.94; 95%-CI [2.14; 7.28]), and insomnia (RR 1.40; 95%-CI [0.92; 2.13]). Adverse effects with weak evidence for nortriptyline were: dizziness, dry mouth, heart burn, orthostatic hypotension, increased appetite, nervousness, palpitations, sedation, sweating, weight gain, and abdominal pain. Blurred vision is the only side effect occurring more frequently under placebo than under nortriptyline with intermediate evidence.
Withdrawal due to adverse effects had a Risk Ratio (RR) of 4.09 (95%-CI [1.31; 12.82]) for treatment with amitriptyline, 0.81(95%- CI [0.12; 5.44]) for treatment with nortriptyline, and 6.31 (95%-CI [1.20; 33.14]) for treatment with desipramine.

Risk ratio (RR) and corresponding 95%-confidence interval (CI) for overall adverse effects and withdrawal due to adverse effects

Effect	Medication	Estimated RR	95%-CI	Strength of evidence
Withdrawal due to adverse effects				
	Amitriptyline	4.09	1.31; 12.82	++
	Nortriptyline	0.81	0.12; 5.44	+–
	Desipramine	**6.31**	**1.20; 33.14**	++
	Milnacipran	**2.28**	**1.87; 2.77**	++
	Venlafaxine	**3.10**	**1.15; 8.35**	++
	Duloxetine	**2.47**	**1.82; 3.36**	++
	Mirtazapine	5	0.25; 98.86	+
	Fluoxetine	1.81	0.2; 16.54	+
Overall adverse effects	Amitriptyline	2.9	0.67; 12.58	+
	Nortriptyline	1.5	0.17; 12.99	+
	Desipramine	**3.77**	**1.33; 10.68**	++
	Milnacipran	1.06	1.00; 1.13	0
	Venlafaxine	**1.44**	**1.03; 2.2**	++
	Duloxetine	1.17	1.06; 1.30	++
	Mirtazapine	2.05	0.54; 7.82	+
	Fluoxetine	**3.78**	**1.25; 11.43**	++

Interpretation of RRs and 95%-CIs are shown as evidence: ++, strong evidence; +, intermediate evidence; +–, inconclusive results; 0, evidence of absence of a clinically relevant effect in either direction (limits for clinical relevance defined as 0.8 < RR < 1.2). Strong evidence + statistical significance for AE/WDR for AD in "bold."

Strengths and limitations of the evidence:

Strengths:

- Tricyclic antidepressants, as a class are supported for use in the treatment of neuropathic pain; there appears to be no difference in efficacy across the class
- Nortriptyline would appear to demonstrate a better adverse event profile than amitriptyline
- Limitations in clinical study data apply to all NP trials including those for amitriptyline

Limitations:

- Clinical studies of the use of nortriptyline in the treatment of neuropathic pain have limited numbers of patients and are of short duration providing low quality evidence
- The NICE Clinical Guideline for the treatment of neuropathic pain in non-specialist settings dose not support nortriptyline use.

Summary of evidence on cost effectiveness:

NICE CG173, issued in November 2013 concluded that nortriptyline's mean cost-per-QALY appeared to represent poor value for money compared with gabapentin and amitriptyline. However, the GDG was mindful that estimates of nortriptyline's effectiveness are highly uncertain. Because of this, it was not possible to exclude the possibility that it may be an extremely effective option and, as a direct

consequence, probabilistic analysis showed that there is a greater than 15% probability that nortriptyline provides the most cost-effective option when QALYs are valued at between £20,000 and £30,000 (which, in the context of pervasive uncertainty, compares well with other options).
The Drug Tariff price for Nortriptyline was significantly higher than that of Amitriptyline and Gabapentin when costings were calculated for CG173, the current cost differential is much smaller – please see table below.[xiv]

Costs of the alternative drugs include in the cost analysis by NICE were from September 2013:

Drug	Drug Tariff price Sept 2013	Drug Tariff price November 2019[c]
Nortriptyline 10mg tablets	£48.55 / 100 tablets[a]	£7.64 / 100 tablets
Nortriptyline 25mg tablets	£74.85 / 100 tablets[a]	£8.78 / 100 tablets
Amitriptyline 50mg tablets	£0.99 / 28 tablets[b]	£2.01 / 28 tablets
Gabapentin 300mg capsules	£3.54 / 100 capsules[b]	£3.22 / 100 capsules
Pregabalin 150mg capsules	£64.40 / 56 capsules[b]	£3.74 / 56 capsules
Duloxetine 60mg capsules	£27.72 / 28 capsules[b]	£2.34 / 28 capsules

[a] verbally confirmed by NHSBSA 27th November 2019
[b] NICE CG173 Costing statement Appendix A
[c] NHS Electronic Drug Tariff November 2019

The difference in the current NHS List Price (November 2019) of Nortriptyline 10mg / 25mg (£0.08 and £0.09 per tablet) and Amitriptyline 50mg (£0.07 per tablet) is minimal.

Prescribing and risk management issues:

Pan Mersey allow the use of nortriptyline for neuropathic pain if amitriptyline is not tolerated.[xv]
This may give rise to problems with cross boundary prescribing, as some of the Lancashire Care clinicians cover pain services in both Southport and Preston.

Commissioning considerations:

Productivity, service delivery, implementation:

N/A

Anticipated patient numbers and net budget impact:

The requesting clinician has advised that the percentage of patients in the catchment area who are referred to their service who are then trialled on nortriptyline if required, would be less than 50 patients per year. They would not expect large numbers a year and all medications are initiated on a strict trial basis with agreement from the patient. Therefore, any nortriptyline use which was deemed inappropriate would be reviewed and stopped within maximum of 4-6 weeks.

The resulting net budget impact would be minimal or cost neutral:

<u>Nortriptyline</u>

At minimum dose of 10mg daily, monthly cost / patient = 28 x £0.08 = £2.24
At maximum dose of 75mg daily, monthly cost / patient = 28 x £0.26 = £7.28 (3x 25mg tablets)

<u>Pregabalin</u>

At recommended starting dose of 75mg twice daily, the monthly cost / patient = £2.67
At maximum recommended dose of 300mg twice daily, the monthly cost / patient = £5.34

<u>Duloxetine</u>

At recommended starting dose of 60mg daily, the monthly cost / patient =£ 2.34
At maximum recommended dose of 60mg twice daily, the monthly cost / patient = £ 4.68

Innovation, need, equity:

There is currently a limited choice of treatments for neuropathic pain in Lancashire and South Cumbria and there is potential inequity between this area and Pan Mersey who allow use of nortriptyline.
This will add another option for patients being referred to a specialist pain service as these patients usually have exhausted other options by this point.

References

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[ii] Drug Tariff November 2019 http://www.drugtariff.nhsbsa.nhs.uk/#/00758525-DD/DD00757937/Part%20VIIIA%20products%20N

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[xi] Neuropathic pain in adults: pharmacological management in non-specialist settings Clinical guideline [CG173] https://www.nice.org.uk/guidance/cg173/evidence/full-guideline-pdf-4840898221

[xii] SPC Nortriptyline 50mg Film-coated Tablets (Glenmark Pharmaceuticals Europe Ltd), Electronic Medicines Compendium, available online: https://www.medicines.org.uk/emc/product/9970/smpc

[xiii] Adverse Effects of Antidepressants for Chronic Pain: A Systematic Review and Meta-analysis Riediger C et al; Front Neurol. 2017 Jul 14;8:307. doi: 10.3389/fneur.2017.00307 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5510574/pdf/fneur-08-00307.pdf

[xiv] NICE, Costing statement - Neuropathic pain in adults: pharmacological management in non-specialist settings https://www.nice.org.uk/guidance/cg173/resources/costing-statement-pdf-191617453

[xv] NEUROPATHIC PAIN GUIDELINES Pharmacological management in non-specialist settings in ADULTS: Pan Mersey 2018 https://www.panmerseyapc.nhs.uk/media/2103/neuropathicpain.pdf