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NICE CLINICAL GUIDELINE 96: *NEUROPATHIC PAIN – THE PHARMACOLOGICAL MANAGEMENT OF NEUROPATHIC PAIN IN ADULTS IN NON-SPECIALIST SETTINGS* (MARCH 2010)

In response to the NICE Clinical Guideline on the treatment of neuropathic pain issued in March 2010, PACEF have been working with ULHT pain specialists to develop Lincolnshire wide guidance.
It is the purpose of this special edition of the *PACE Bulletin* is to summarize the key points of the local guidance.

Executive Summary

Neuropathic pain including painful diabetic neuropathy

- **Offer oral amitriptyline first line; start at 10mg daily and titrate up gradually to an effective dose or the person's maximum tolerated dose of no higher than 75mg per day (higher doses may be considered in consultation with the specialist pain service).**
- **If the patient's pain responds to amitriptyline, but poor tolerability is a problem, consider nortriptyline as an alternative tricyclic antidepressant (TCA).**
- **If satisfactory pain reduction is not achieved with amitriptyline (or nortriptyline as an alternative), gabapentin capsules are recommended second line.**
- **Pregabalin capsules (Lyrica) are a preferred alternative to gabapentin in the elderly.**
- **Where gabapentin or pregabalin have been insufficiently effective or poorly tolerated, duloxetine (Cymbalta) is recommended third line.**
- **If satisfactory pain reduction is not achieved (1) refer the person to a specialist pain service and or condition-specific service and (2) while waiting for referral consider oral tramadol instead of or in combination with second line/third line treatment. Where tramadol is indicated, standard release tramadol capsules should be preferred.**
- **Do not start treatment with opioids (e.g. morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service.**
- **Consider lidocaine medicated plaster 5% (Versatis) as a fourth line option for the treatment of all types of neuropathic pain for people who are unable to take oral medication because of medical conditions and/or disability. Initiation of treatment with lidocaine plasters should only be on the *advice* of a secondary care based specialist (this includes consultants and nurse specialists from the pain service and consultants from other specialities such as orthopaedics and rheumatology). Initiation on specialist advice can be undertaken following a written or telephone request and does not necessarily require formal referral to the pain service.**

Introduction

In response to the NICE Clinical Guideline on the treatment of neuropathic pain issued earlier in the year, PACEF have been working with ULHT pain specialists to develop Lincolnshire wide guidance. The over riding principle behind the review of local guidance is to enhance and improve the patient experience. The Lincolnshire-wide guidance differs in some aspects from the NICE CG; where differences occur, this is highlighted in the text.

General principles of care

- Consider referring to a specialist pain service and/or a condition-specific service at any stage, including at initial presentation and at regular clinical reviews if: (1) the patient has severe pain or (2) their pain significantly limits their daily activities and participation or (3) their underlying health condition has deteriorated.
- Continue existing treatments for people whose neuropathic pain is already effectively managed.
- When selecting pharmacological treatments, take into account: the person's vulnerability to specific adverse effects due to co-morbidities; safety considerations and contraindications; patient preference; lifestyle factors (such as occupation), any mental health problems; other medication the person is taking.
- Explain the importance of dose titration and the titration process.
- When withdrawing or switching treatment, taper the withdrawal regimen to take into account dosage and discontinuation symptoms.
- When introducing a new treatment, consider overlap with the old treatments to avoid deterioration of pain control.
- Perform regular clinical reviews to assess and monitor the effectiveness of the chosen treatment. Each review should include assessment of pain reduction, adverse effects, daily activities and participation, mood, quality of sleep and overall improvement.

The NICE Clinical Guideline differentiated between the management of painful diabetic neuropathies and neuropathic pain from other causes. The ULHT pain service have recommended that all types of neuropathic pain can be initially managed using the same treatment pathway.

Neuropathic Pain (including painful diabetic neuropathies): First line treatment

- NICE recommend either oral amitriptyline or pregabalin as first-line treatment.

PACEF and ULHT Pain Services Recommendations: First Line Amitriptyline

Existing local guidance recommends first line amitriptyline 10mg daily titrated up gradually to an effective dose or the person's maximum tolerated dose of no higher than 75mg per day (higher doses may be considered in consultation with the specialist pain service). A trial of 3 months at the effective or maximum tolerated dosage is advised. If the patient's pain responds to amitriptyline, but poor tolerability is a problem, consider nortriptyline as an alternative tricyclic antidepressant (TCA). Nortriptyline should be titrated up gradually from a starting dose of 10mg daily up to 75mg daily (higher doses may be considered under specialist supervision).

The NICE Guidelines Development Group (GDG) acknowledge that the majority of the evidence for TCAs in the treatment of neuropathic pain is for amitriptyline. This provides the basis for their recommendation that it should be used first or second line despite the fact that amitriptyline is not licensed for this indication. Amitriptyline should also be considered first line on the grounds of cost; pregabalin is over 60 times the cost of generic amitriptyline and should not be considered first line in most patients (see cost comparison). Cautions and contra-indications to the use of TCAs are summarised below.

	Dose	Cost for 28 days treatment
Amitriptyline 10mg tablets (generic)	**10mg daily**	**£0.96**
Amitriptyline 25mg tablets (generic)	**25mg daily**	**£0.92**
Amitriptyline 50mg tablets (generic)	**50mg daily**	**£1.01**
Pregabalin caps (Lyrica)	**75mg twice daily to 300mg**	**£64.40**

	twice daily	

(Prices derived from *Drug Tariff* February 2011)

Tricyclic antidepressants: Cautions and Contra-indications

Tricyclic antidepressants should be used with **caution** in patients with:

Cardiovascular disease
Hyperthyroidism
Phaeochromocytoma
Epilepsy
Diabetes
Prostatic hypertrophy
Chronic constipation
Increased intra-ocular pressure
Urinary retention
Susceptibility to angle-closure glaucoma
Significant risk of suicide
History of psychosis or bipolar disorder

TCAs are **contra-indicated** in patients with:

Arrhythmias
Heart block
Manic phase of bipolar disorder
In the immediate recovery period after MI
Acute porphyria

Neuropathic Pain (including painful diabetic neuropathies): Second Line Treatment

NICE Recommendations

- If satisfactory pain reduction is not achieved with amitriptyline (or nortriptyline as an alternative), a drug from another therapeutic class (i.e. an anti-epileptic) should be recommended second line.
- NICE acknowledge evidence (of high to moderate quality) for the efficacy of both pregabalin and gabapentin in the treatment of neuropathic pain.
- Pregabalin and gabapentin have similar pharmacological profiles (high affinity for the alpha-2-delta subunit of the voltage dependent calcium channel in the CNS); **it is highly unlikely that a patient will have an unsatisfactory response with one drug, but achieve pain reduction with the other**
- Ultimately, NICE advocate pregabalin as the preferred alternative to gabapentin for the following reasons: (1) Evidence from indirect comparisons of meta-analyses showed that pregabalin has lower Numbers Needed to Treat (NNT) values for at least 30% pain reduction and at least 50% pain reduction compared with gabapentin (and a similar adverse effect profile); (2) Pregabalin has simpler dosing and dose titration than gabapentin; and (3) Cost effectiveness modelling showed pregabalin to be more cost-effective than gabapentin.

PACEF and ULHT Pain Services Recommendations: Second Line Gabapentin capsules

Unfortunately, NICE cost effectiveness modelling that showed pregabalin to be more cost-effective than gabapentin was compromised by the inadvertent omission of low cost gabapentin capsules from the model. NICE have acknowledged this error on their website and are currently reviewing the cost-model with a view to publishing revised conclusions. The cost comparison below reveals the scale of the price difference between gabapentin capsules and tablets, particularly at the 800mg strength. As a result of this, gabapentin capsules are the recommended anti-epileptic of choice to be used second line after a TCA. Gabapentin should be initiated at 300mg once daily and the dose titrated up by 300mg every three days according to response (i.e. 300mg daily > 300mg twice daily > 300mg three times daily > 300mg twice daily plus 600mg at night > 600mg twice daily plus 300mg daily > 600mg three times daily). Gabapentin tablets are prohibitively expensive and should not be routinely prescribed; pregabalin capsules are even more expensive and should only be considered as detailed below.

	Dose	Cost for 28 days treatment
Gabapentin 300mg capsules (generic)	**One three times daily**	**£9.42**
Gabapentin 300mg capsules (generic)	**Two (600mg) three times daily**	**£18.84**
Gabapentin 400mg capsules (generic)	**Two (800mg) three times daily**	**£12.03**
Gabapentin 600mg tablets (generic)	One (600mg) three times daily	£19.92
Gabapentin 800mg tablets (generic)	One (800mg) three times daily	£32.87
Pregabalin 75mg)capsules (Lyrica)	75mg twice daily to 300mg twice daily	£64.40

(Prices derived from *Drug Tariff* February 2011)

PACEF and ULHT Pain Services Recommendations: Second Line Pregabalin

Pregabalin capsules are a preferred alternative to gabapentin in the elderly. For dose titration, start at 150mg per day (divided into 2 doses) with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 600mg per day (divided into 2 doses); a lower starting dose may be appropriate in the elderly. Pregabalin (Lyrica) is licensed for peripheral and central neuropathic pain and is designated GREEN for these indications subject to the criteria outlined above.

Neuropathic Pain (including painful diabetic neuropathies): Third-line treatment

PACEF and ULHT Pain Services Recommendations: Third-line Duloxetine

Where gabapentin or pregabalin have been insufficiently effective or poorly tolerated, duloxetine (Cymbalta) is recommended third line. For duloxetine, start at 60mg a day (or lower depending on the patient) with upward titration to an effective dose or the person's maximum tolerated dose (no higher than 120mg per day). If there is improvement, continue the treatment; consider gradual reduction of the dose over time if improvement is sustained. Duloxetine (Cymbalta) is licensed for the treatment of painful diabetic neuropathy, but is advocated off license as a third line option for the general management of neuropathic pain by ULHT Pain Services.

NICE Recommendations

- The NICE Clinical Guideline differentiates between the management of diabetic neuropathies and the general management of neuropathic pain and recommends oral duloxetine as a first line option in the management of painful diabetic neuropathy. In order to simplify the pathway, neuropathic pain and painful diabetic neuropathy have been amalgamated into a single pathway on the advice of ULHT Pain Services.
- Whilst duloxetine is cheaper than pregabalin at standard therapeutic doses, there is more published evidence to support use of pregabalin in preference; duloxetine should only be considered where gabapentin or pregabalin have not proved effective or are contraindicated.

Duloxetine: Cautions and Contra-indications

Duloxetine should be used with caution in the elderly and patients with::

cardiac disease
hypertension
history of mania
history of seizures
raised intra-ocular pressure
susceptibility to angle closure glaucoma
bleeding disorders
concomitant use of drugs that increase risk of bleeding

Duloxetine is contra-indicated in:

uncontrolled hypertension
hepatic impairment
severe renal impairment (eGFR less than 30ml/min/1.73m^2)
pregnancy and breast feeding

PACEF and ULHT Pain Services Recommendations: Combination therapy

General NICE advice on the use of combination therapy is supported, although amitriptyline should be used first line and gabapentin capsules in preference to pregabalin or duloxetine (as detailed above). The NICE CG states that, if satisfactory pain reduction is not achieved with first line treatment at maximum tolerated dose, offer treatment with another drug instead of or in combination with the original drug.

Neuropathic Pain (including painful diabetic neuropathies): Fourth-line treatment

- If satisfactory pain reduction is not achieved (1) refer the person to a specialist pain service and or condition-specific service and (2) while waiting for referral consider oral tramadol instead of or in combination with second line/third line treatment. Where tramadol is indicated, standard release tramadol capsules should be preferred.
- Do not start treatment with opioids (e.g. morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service.
- Consider lidocaine medicated plaster 5% (Versatis) as a fourth line option for the treatment of all types of neuropathic pain for people who are unable to take oral medication because of medical conditions and/or disability. Initiation of treatment with lidocaine plasters should only be on the *advice* of a secondary care based specialist (this includes consultants and nurse specialists from the pain service and consultants from other specialities such as orthopaedics and rheumatology).

PACEF and ULHT Pain Services Recommendations: Oral Tramadol

The NICE GDG considered the evidence of efficacy of opioid analgesics (e.g. tramadol, morphine and oxycodone) for the treatment of neuropathic pain to be of moderate to low quality and lacking reliability. Ultimately, tramadol is recommended as a third line/fourth line treatment for neuropathic pain rather than morphine due to the lower withdrawal rates with tramadol in comparative trials with morphine and the lower incidence of constipation. Where tramadol is indicated, standard release generic tramadol capsules are advocated on grounds of cost (see cost comparison).

	Dose (200mg daily chosen as standard caomparator dose)	**Cost for 28 days treatment**
Standard Release		
Tramadol 50mg caps (generic)	**50mg four times daily**	**£2.37**
Tramadol 50mg caps (Zamadol)	**50mg four times daily**	**£8.79**
Tramadol 50mg orodispersible tabs (Zamadol Melt)	**50mg four times daily**	**£13.02**
Tramadol 50mg caps (Zydol)	**50mg four times daily**	**£7.48**
Tramadol 50mg soluble tabs (Zydol Soluble)	**50mg four times daily**	**£13.05**
Modified Release		
Tramadol 200mg tabs (Tradorec XL)	200mg once daily	£13.98
Tramadol 100mg SR (Zamadol SR)	100mg twice daily	£13.99
Tramadol 200mg SR (Zamadol 24hr)	200mg once daily	£13.99
Tramadol 100mg SR tabs (Zydol SR)	100mg twice daily	£17.04
Tramadol 200mg SR tabs (Zydol XL)	200mg once daily	£16.78

(Prices derived from *Drug Tariff* February 2011 and *MIMS* November 2010)

PACEF and ULHT Pain Services Recommendations: Topical Lidocaine

At present, lidocaine medicated plaster 5% (Versatis) is only licensed for post-herpetic neuralgia and not for the broader context of neuropathic pain. The ULHT Pain Service have asked PACEF to designate lidocaine medicated plaster 5% (Versatis) as AMBER for ALL types of neuropathic pain (assuming a fourth line role). Treatment should only be started following *advice* from the specialist service, and consultants from other specialities. Initiation on specialist advice can be undertaken following a written or telephone request and does not necessarily require formal referral.

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