Pharmacological Treatment of Neuropathic Pain

County Durham and Darlington
Area Prescribing Committee

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SCOPE

The purpose of this document is to provide prescribers with guidance on the pharmacological treatment of neuropathic pain. The guidance should be read in conjunction with the key messages document detailed below.

The guidelines and key messages (Treatment of Neuropathic pain, Strong Opioids and Tapering Opioids) have been developed by the County Durham and Darlington Pain Prescribing Guidelines Task and Finish Group; a sub group of the County Durham and Darlington Area Prescribing Committee and comprised of members from County Durham and Darlington Foundation Trust, North Durham CCG, Durham Dales Easington & Sedgefield CCG and North of England Commissioning Support. The key messages (Managing Persistent Pain and Non-pharmacological Management of Pain) have been approved by both the County Durham and Darlington Pain Management Education Group and also the Pain Management Project Group.

The guidelines:

- Pharmacological Treatment of Neuropathic Pain
- Opiate Prescribing in Persistent (Non-cancer) Pain [link to add]

Key Messages: [link to add]

- Managing Persistent Pain
- Non-pharmacological Management of Pain
- Treatment of Neuropathic Pain
- Strong Opioids
- Tapering Opioids for Persistent Pain

All references are provided as a guide and individual patient factors should be taken into account before a change to treatment is initiated.

Please refer to the BNF or Summary of Product Characteristics for further information on medications, side effects, cautions, contra-indications, interactions and formulations.

INTRODUCTION

Neuropathic pain is a common chronic pain condition that can be difficult to treat. The International Association for the Study of Pain defines this as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'. A range of conditions can lead to this disruption or alteration of the peripheral or central nervous system for example, peripheral diabetic neuropathy or multiple sclerosis. The condition may also be mixed with inflammatory pain, for example sciatica. Early studies suggested prevalence to be around 1% of the UK population, more recent research in 2006 estimates this figure to be around 8%.[(1)]

This guideline was developed to establish a local unified approach to management of chronic neuropathic pain for non-specialist prescribers and regional specialists in chronic pain.

It aims to provide an accessible and readable document which will improve the safety, quality and cost effectiveness of prescribing in primary and secondary care through an evidence based series of management options. The advice provided is based upon the latest clinical evidence and adapting it to include treatments based on clinical experience.

It has been developed by the County Durham and Darlington Pain Prescribing Guidelines Task and Finish Group; a sub group of the County Durham and Darlington Area Prescribing Committee and comprised of members from County Durham and Darlington NHS Foundation Trust, North Durham CCG, Durham Dales Easington & Sedgefield CCG and North of England Commissioning Support.

The treatment pathway can be found on page 4 with further information on each treatment option linked and detailed later in the document.

There is also specific information on the following conditions, where these are the suspected diagnosis, please check the relevant section first:-

Trigeminal Neuralgia
Post Herpetic Neuralgia
Painful Diabetic Neuropathy

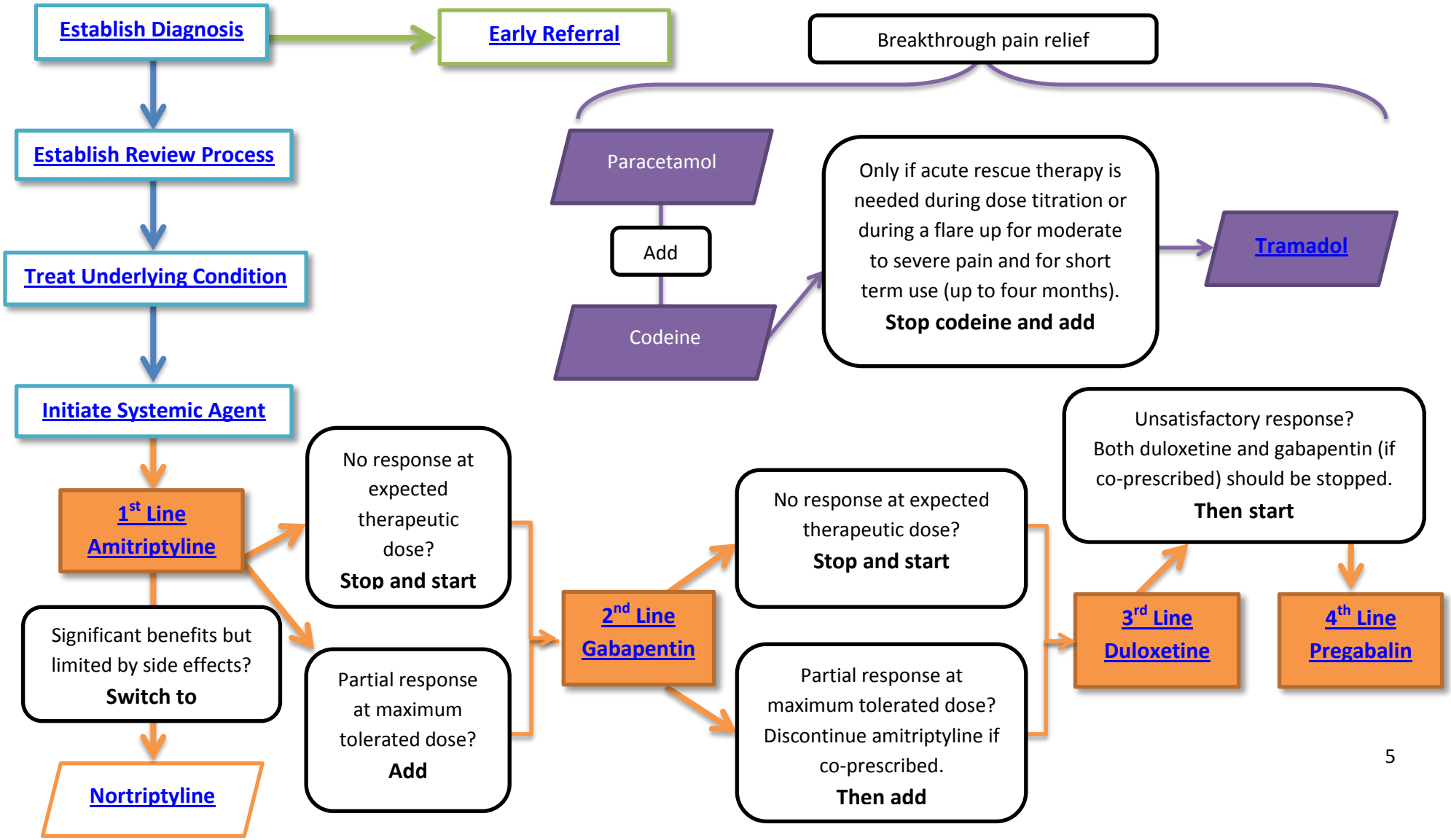
Strong Opiates - strong opiates should not be commenced outside the specialist setting in the management of chronic neuropathic pain (this does not apply to palliative pain management). Tramadol – a weaker opioid - may be used and is included in the pathway.

Many of the agents used in the management of chronic neuropathic pain are also drugs of abuse and have significant 'street value' attributed to them. NHSE and Public Health England have issued advice for prescribers on the misuse of pregabalin and gabapentin that can be accessed here. It is widely accepted that a

proportion of the illegal supply is sourced by diversion of legitimate prescriptions from primary and secondary care. Vigilance is advised in at risk patients. You may find some useful information in this NHS England document “Pain Management Formulary for Prisons” linked here; there are significant differences in the approach to this patient group.

Neuropathic Pain Pathway

The key goal is to improve patient function. This may be achieved by progressing control of pain to the point at which it is managed satisfactorily or resolves. To achieve this goal, specialist secondary care assessment and intervention may be required. Patients should also be aware that the pain may never completely resolve.



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ESTABLISH A CLEAR DIAGNOSIS

Diagnosis of neuropathic pain is a clinical diagnosis but may be aided by one of the various available questionnaires.

A self-reported version of 'The Leeds Assessment of Neuropathic Symptoms and Signs pain scale', known as the S-LANSS score, aims to identify pain of predominantly neuropathic origin, as distinct from nociceptive pain, without the need for clinical examination. This has been endorsed as a useful tool by the guideline panel and is attached in Appendix 1.

Once diagnosis is made, it is usual practice to start an initial systemic drug.

CRITERIA FOR EARLY SPECIALIST REFERRAL

Consider referring the person to a specialist pain service and/or a condition-specific service at any stage, including at initial presentation and at the regular clinical reviews if; there is diagnostic uncertainty, patient has severe pain, pain significantly limits daily activities (including sleep disturbance and participation in activities) or the underlying health condition has deteriorated. Continue to work through neuropathic pain pathway whilst waiting.

ESTABLISH A REVIEW PROCESS

Review should be frequent, two weeks after initiating treatment is advised. This allows: (i) assessment of the effectiveness of treatments in symptom improvement; (ii) safe titration of doses as required; and (iii) assessment of any adverse reactions. In most cases, the starting dose will be lower than the effective dose and the maximum tolerated effective dose, early review will minimise the interval to this and therefore reduce suffering and improve treatment success. Drugs that are having little useful effect after a dose titration to the expected effective dose should be stopped and an alternative tried.

TREAT THE UNDERLYING CONDITION

Optimise management of the underlying condition e.g. blood sugar control in painful diabetic neuropathy.

INITIATE A SYSTEMIC AGENT

Common clinical practice is to use a tricyclic antidepressant (TCA) or gabapentinoid for the treatment of neuropathic pain and the pathway recommends amitriptyline as 1st line choice. If the first agent chosen is not helpful, then an alternate may be used either as a sole agent or in combination as discussed in the pathway.

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Individual patient factors must be considered when identifying the most appropriate medication to prescribe, as some patients may have conditions in which the treatments recommended in the pathway would be contra-indicated for use in.

The British National Formulary and individual drug Summaries of Product Characteristics should be checked for a detailed list of contraindications, cautions, side effects and interactions. Included are some helpful practice points, and advice based on clinical experience, in the summaries below.

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AMITRIPTYLINE

Amitriptyline is a tricyclic antidepressant (TCA). Its use in pain is an unlicensed indication but it has a long history of therapeutic value. Number needed to treat for 50% pain reduction compared to placebo (NNT) is 3; number needed to harm (NNH) is 14.7.[(2)]

Particular caution should be given to initiating in the elderly as they are more susceptible to side effects. Concomitant use with duloxetine (and other SNRIs) can increase side effects, holds a risk of serotonin syndrome and a risk of QT interval prolongation. Their use in combination is not advised.

Dosing

Start with 10mg taken at night. Increase slowly by 10mg per week. Suggested amitriptyline dose range for efficacy is 25mg; continue titration to 75mg if required and as tolerated.

Side effects

TCAs have anticholinergic side effects. One of the common reasons for discontinuation is excessive drowsiness. Other side effects include sedation (caution with driving), constipation, confusion, glaucoma, falls, visual disturbance, orthostatic hypotension, and urinary retention: caution in elderly or those with dysrhythmias.

Cost

For one year of treatment at 25mg daily £10.27 (RDTC Jan 2017)

Additional information

A patient information leaflet is available from the British Pain Society and can be downloaded from the following link.

Information for Adult Patients Prescribed Amitriptyline for the Treatment of Pain

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NORTRIPTYLINE

The TCA nortriptyline may have a lower side effect profile than amitriptyline as it is less anticholinergic. There is no evidence of increased efficacy. Consider a change to nortriptyline in those who have benefitted from amitriptyline but have been limited by tolerability.

Dosing

The same titration schedule as for amitriptyline can be followed, however the maximum dose advised is 75mg daily.

Cost

The annual cost is significantly higher. For one year of treatment at 25mg daily £115.46 (RDTC Jan 2017)

Additional information

A patient information leaflet is available from the British Pain Society and can be downloaded from the following link.

Information for Adult Patients Prescribed Nortriptyline for the Treatment of Pain

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GABAPENTIN

Gabapentin holds a license for use in peripheral neuropathic pain; evidence that the NNT is 5.1, and the NNH is 26.1.[2]

Caution when used in those patients with any degree of renal impairment. Caution also in those with diabetes as it may affect blood glucose readings, although commonly used in this patient group.

Dosing

Consider patient factors when commencing a dosing regimen. Starting at lower doses can minimise side effects but will delay time to reaching an effective dose. A number of dosing schedules are available and the dose should be titrated according to tolerability and efficacy.

Suggested regimens are included in *Appendix 2*.

Note that if 300mg is poorly tolerated as a starting dose, gabapentin can be started at a much lower dose, and increased more gradually.

The BNF states a more rapid titration with 300mg once daily on day one, then 300 mg twice daily on day two, then 300 mg three times a day on day three or alternatively initially 300 mg three times a day on day one, then increased in steps of 300 mg every two to three days in three divided doses. In practice this regimen is limited by side effects, therefore it should be reserved for use in a restricted patient group of particularly fit, healthy adults who have a clear understanding of the titration process and potential side effects, including drowsiness which may affect their ability to drive.

Evidence suggests that a minimum of 1,200mg daily is needed. Doses may need to be increased as high as 3,600mg. This is consistent with published clinical trials.

Side effects

Drowsiness, weight gain, dizziness, fatigue and muscle tremor.

Cost

For one year of treatment at (2x300mg three times a day) £61.59 (RDTC Jan 2017)

Additional information

Although licensed as three times a day dosing, clinical practice has shown that side effects can be reduced by using a dosing schedule of four times a day, taken with food, with a larger dose used at night. Please take care to ensure maximum daily dose is not exceeded if patients are using four times a day dosing.

A patient information leaflet is available from the British Pain Society and can be downloaded from the following link.

Information for adult patients prescribed gabapentin for the treatment of pain

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DULOXETINE

Duloxetine belongs to the group of medicines called Serotonin Noradrenergic Reuptake Inhibitors (SNRI). Originally used as an antidepressant, it has demonstrated evidence of benefit in painful diabetic peripheral neuropathy - see relevant section of pathway. It may also be beneficial as an alternative to first line agents in other types of neuropathic pain. It is thought to work by increasing activation of the inhibitory neural pathways.

Its use is not recommended in patients with unstable hypertension or liver disease and should be used with caution in those with a history of seizures.

Dosing

Start at 30mg daily for one week, and then titrate up to 60mg daily. Doses of up to 120mg have been used.

Side effects

Commonly reported; headache, drowsiness, sickness (nausea), dizziness, blurred vision and dry mouth.

Cost

For one year of treatment at 60mg daily £30.81 (RDTC Jan 2017)

Additional information

May be of added benefit where depression is thought to be a contributory factor.

If sedation occurs, advise patient to take at night.

A patient information leaflet is available from the British Pain Society and can be downloaded from the following link.

Information for Adult Patients Prescribed Duloxetine for the treatment of pain

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PREGABALIN

Pregabalin is an alternative treatment in patients who have failed on or not tolerated amitriptyline and gabapentin. It does not have a therapeutic advantage over gabapentin and NNT is 3.7 and NNH is 7.4.[2] The longer half-life and bioavailability allow twice daily dosing. It can be started at a dose of 75 mg twice daily. In some patients, smaller starting doses may be used but doses below 150 mg daily are generally ineffective. Pregabalin may be titrated up until a maximum dose of 300 mg twice daily is reached. A titration regime is suggested below. The dose should be titrated according to tolerability and efficacy.

Dosing

Suggested pregabalin dosing schedule

Week	Breakfast	Night
Week 1	50mg	50mg
Week 2	75mg	75mg
Week 3	150mg	150mg
Week 4	300mg	300mg
Continue titration to efficacy / tolerability limit		

Side effects

Common side effects are somnolence (caution with driving), dizziness and weight gain.

Cost

Please refer to the drug tariff for current pregabalin pricing.

Additional information

Pregabalin is also licensed for use in the treatment of generalised anxiety disorder (GAD). As our current understanding of pain perception recognises that anxiety about pain can increase the pain experience, it could be worth considering other approaches to anxiety management in patients who show benefit to pregabalin being used for neuropathic pain control.

A patient information leaflet is available from the British Pain Society and can be downloaded from the following link.

Information for Adult Patients Prescribed Pregabalin for the treatment of pain

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TRAMADOL

Tramadol hydrochloride is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

The pathway recommends the short term use (up to four months) of tramadol, for moderate to severe pain, after a trial of paracetamol and codeine if acute rescue therapy is needed during dose titration or during a flare up.

Prescribers are reminded that tramadol is a schedule three controlled drug due to an increasing number of deaths relating to its misuse.

Tramadol is not recommended for long term use.

Dosing

50mg–100mg every four to six hours, maximum of 400mg daily. Consider lower doses in at risk populations. Elimination half-life is increased in those aged over 75, consider longer dose intervals and a lower maximum dose.

Treatment cessation

A suggested approach would be to reduce the dose by 50 mg at a time, whilst keeping the dosing frequency the same. However, there are no studies to inform this and patients would need to be monitored closely. [3]

Side effects

As for opioid analgesics in general, however tramadol may produce fewer typical opioid adverse effects such as respiratory depression and constipation.

Deaths associated with tramadol use have been reported in patients with a history of emotional disturbances, suicidal ideation or attempted suicide, or misuse of CNS depressants such as alcohol and anxiolytics.

Cost

Tramadol 50mg capsules - eight daily for seven days treatment £1.61 (RDTC Jan 2017) (£83 per year)

Additional information

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity. It is more likely to occur at higher dose ranges. At risk patients should be counselled of the symptoms (such as fever, tremors, diarrhoea, and agitation). Concurrent treatment should be stopped if symptoms occur.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions.

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TRIGEMINAL NEURALGIA

Carbamazepine taken during the acute stages of trigeminal neuralgia reduces the frequency and severity of attacks. Satisfactory pain relief may be achieved in 70% or more of patients. Carbamazepine should be commenced as the first line agent. If this is contraindicated, ineffective, or there are intolerable side effects, consider early referral for neurosurgical advice and commence alternative agent as for neuropathic pain such as gabapentin.

CARBAMAZEPINE

Suggested carbamazepine dosing schedule

Week	Breakfast	Lunch	Evening	Night
Day 1				100mg
Day 2, 3, 4	100mg			100mg
Day 5, 6, 7	100mg			200mg
Day 8, 9, 10	200mg			200mg
Continue titration to efficacy / tolerability limit				

Please note that a slower titration regime could be considered in those felt to be at particular risk of poor tolerance. For single doses lower than 100mg, a liquid formulation will be required.

In the majority of people, a dosage of 200 mg three or four times a day is sufficient to prevent paroxysms of pain (maximum dosage 1600 mg daily).

Side effects

Common side effects include dizziness, drowsiness, fatigue, nausea, and headache.

Rare, but potentially serious blood and skin disorders can occur. Inform the patient to contact their doctor immediately if they get any of the following:- a rash or peeling of the skin, mouth ulcers or unexplained bleeding or bruising, a persistent sore throat, high temperature, yellowing of the eyes or skin, significant abdominal pains, or any change in mental state.

Monitoring

Serum sodium levels should be measured prior to initiating carbamazepine therapy, after approximately two weeks of treatment

and then at monthly intervals for the first three months during therapy, or according to clinical need.

The manufacturer recommends full blood count, hepatic function and renal function tests to be completed before treatment and periodically thereafter. For serum levels, the BNF states the practical value of this monitoring is uncertain. Clinical monitoring is of greater value and patients should be counselled thoroughly to be vigilant of warning signs.

Cost

For one year of treatment at 200mg four times daily £66.39 (RDTC Jan 2017)

Additional information

Modified release preparations may be useful at night if the person experiences breakthrough pain.

When pain is in remission, consider reducing the dose, if the person remains pain free for 1 month, consider gradually withdrawing the drug.

Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of the active metabolite of carbamazepine. Also carbamazepine itself is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems; therefore there is significant potential for drug-drug interactions. All concomitant medications should be reviewed prior to initiation and at any dose change, cessation or addition of medication.

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POST HERPETIC NEURALGIA

Post-herpetic neuralgia is a chronic, debilitating pain in a dermatomal distribution that persists after healing of shingles rash, and is caused by herpes zoster-induced peripheral-nerve damage.

General advice and information is available from the NICE clinical knowledge summaries.

Patient information leaflets are available from the British Association of Dermatologists.

Offer paracetamol with or without codeine if the person's pain is mild or moderate, and there are no contraindications.

Consider prescribing lidocaine plasters. **This is the only licensed indication for lidocaine patches, and the only situation indicated by this advisory group**. They have a better side effect profile than oral medication, particularly in the elderly or in those where central nervous system side effects are a concern.

If pain remains uncontrolled, consider offering a drug to treat neuropathic pain, following the pathway detailed above. Lidocaine plaster may be continued an adjunct to oral therapy if pain is severe.

LIDOCAINE 5% MEDICATED PLASTER

Dosing

The painful area should be covered with a plaster once daily for up to 12 hours within a 24 hour period. The subsequent plaster-free interval must be at least 12 hours.

The plasters may be cut into smaller sizes with scissors prior to removal of the release liner. No more than three plasters should be used at the same time.

Review effect after two weeks. If there has been no response discontinue. Treatment should continue to be reassessed at regular intervals. The amount of plasters needed to cover the painful area can be reduced with time, or the plaster-free period can be extended.

Side effects

Approximately 16% of patients can be expected to experience adverse reactions. The most commonly reported adverse reactions were

administration site reactions (such as burning, dermatitis, erythema, pruritus, rash, skin irritation, and vesicles).

Cost

For one year of treatment at one patch daily £878.45 (RDTC Jan 2017)

Additional information

The off license use of lidocaine plasters has been a significant prescribing cost burden both locally and nationally, prescribers are asked to review efficacy and indication regularly. The position of the guideline development group is that lidocaine patches are not to be used outside their licensed indications.

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PAINFUL DIABETIC NEUROPATHY

A local stepwise approach to management is advised by pain specialists in secondary care as below:-

Commence amitriptyline; consider a change to nortriptyline if indicated.

If ineffective, change to duloxetine as above.

If ineffective change to gabapentin as above.

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Appendix 1 – S-LANSS Questionnaire

LANNS-NP-Assessment-Tool-only.pdf

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Appendix 2 – Gabapentin Dosing Schedules adapted from Lancashire Medicines Management Group

The BNF suggests an accelerated titration regimen i.e. starting at 300mg three times per day and increasing by 300mg every 2-3 days according to response.
In practice this regimen is limited by side effects, therefore it should be reserved for use in a restricted patient group of particularly fit, healthy adults who have a clear understanding of the titration process and potential side effects, including drowsiness which may affect their ability to drive.

Standard Gabapentin dosing schedule:

Day	Breakfast	Evening Meal	Night
1	0	0	300mg
2	300mg	0	300mg
3, 4	300mg	300mg	300mg
5, 6	300mg	300mg	600mg
7, 8	300mg	600mg	600mg
9, 10	900mg	600mg	600mg
Day 11 onwards: doses may be increased by 300mg/day, at 3 day intervals up to a maximum of 3600mg daily. Doses should be titrated according to response and tolerability.			

Beneficial effects should be demonstrated by week five of treatment.

For elderly patients or those who are sensitive to gabapentin where 300mg is poorly tolerated as a starting dose, gabapentin can be started at a much lower dose, and increased more gradually. We recommend the following dosing schedule in this case:

Days	Breakfast	Evening Meal	Night
1, 2, 3	0	0	100mg
4, 5, 6	100mg	0	100mg
7 - 13	100mg	100mg	100mg
14 - 20	200mg	200mg	200mg
Day 21 onwards: dose may be increased by 300mg/day, ideally at weekly intervals as tolerated up to a maximum of 3600mg daily. Doses should be titrated according to response and tolerability.			

REFERENCES

1) B. H. Smith, J. Lee, C. Price and A. P. Baranowski. *Neuropathic pain: a pathway for care developed by the British Pain Society* [Internet]. 2013 [Cited 09 August 2017]; British Journal of Anaesthesia 111 (1): 73–9 (2013) doi:10.1093/bja/aet206

2) N. B. Finnerup, M. Otto, T. S. Jensen And S. H. Sindrup. *An Evidence-Based Algorithm For The Treatment Of Neuropathic Pain* [Internet]. 2007. [Cited 23 August 2017]; Medscape General Medicines.

3) Trent Medicines Information Centre. *Tramadol: New Legal Classification [Internet]*. 2014 [Cited 23 August 2017]. UK Medicines Information.