Guidelines for the Management of Neuropathic Pain

Introduction

- Neuropathic pain can be described as numbing with burning, shooting or tingling sensations.[1, 2]
- Patients should be advised that a totally pain free status is not always achievable. The commonly used endpoint in trials is reduction in pain by 50%. Coping strategies, anxiety and depression should also be addressed at the same time as pain control.
- The common types of neuropathic pain are post herpetic neuralgia (PHN) caused by herpes zoster and painful diabetic neuropathy.[3] Cancer-related pain may have a neuropathic mechanism involved.[4]
- Many products are not specifically licensed for neuropathic pain and it is important to advise patients of this.
- Capsaicin cream 0.075% may be of benefit for localised treatment, in line with licensed indications.[2]
- Lidocaine 5% medicated plasters are recommended only as a fourth line option for severe PHN pain which is not responsive to, or where the patient cannot tolerate, other agents; in line with the agreed treatment pathway for patients presenting with shingles (*Appendix 1*).
- Capsaicin patches are recommended for severe PHN only in non-diabetic patients, following lidocaine 5% patch failure (i.e. fifth line within *Appendix 1*); for use (following the relevant training) by a secondary care physician or health care professional under the supervision of a physician in line with the manufact. SPC.
- Other physical treatments such as Transcutaneous Electrical Nerve Stimulation (TENS) may be of benefit and can be used concurrently. NB: NICE Clinical Guideline 88 (May 2009) does not support TENS for low back pain.

Drug Choices and Doses *Refer to the relevant SPC with regards to dosing, cautions, contra-indications, interactions and side-effect profile to ensure the most current information is referred to.*

Drug	Initial daily dose	Maximum daily dose	Notes
Step 1 Tricyclics			
1. Amitriptyline*	10-25mg	75mg daily	Start with a low dose and titrate up to the maximum tolerated or recommended dose before treatment failure is confirmed.[2] *Amitriptyline has a good clinical evidence base supporting its use for treating diabetic neuropathy.
2. Nortriptyline	10-25mg	75mg daily	As amitriptyline.
Step 2 Anticonvulsants			
1. Carbamazepine	100mg 1- 2 times daily	800mg daily	Increase slowly to 200mg 3 - 4 times daily. Licensed for trigeminal neuralgia only.
2.Gabapentin capsules (not tablets)	300mg	3600mg daily	Increase by 300mg every day for three days then in increments of 300mg every 2-3 days to a max of 3600mg daily. Advise patient to avoid abrupt withdrawal – taper off over at least 1 week. See initiation / dose titration leaflet
Step 3 Combination of a tricyclic antidepressant **and** traditional anticonvulsant			
			This combination is recommended as Step two of a treatment ladder described by Twycross.[5]
Step 3 Specifically for diabetic neuropathy ONLY			
Duloxetine	60mg	60mg daily**	**In trials a total daily dose of 120mg (60mg twice daily) was not found to be superior to 60mg per day.[6] Response is seen within one week and unlikely if not seen by eight weeks.
Step 4 Newer anticonvulsants – Pregabalin			
Pregabalin capsules	25mg twice daily	300mg twice daily***	**NB only use if gabapentin fails or is not tolerated.** Start with a dose of 25mg twice daily; the dose should be titrated according to patient response to 300mg twice daily if needed. Advise patient to avoid abrupt withdrawal – taper off over at least 1 week. If not effective after 7 days then stop. ***To greatly increase cost effectiveness, only use twice daily dosage rather than three times daily.
Step 5 Opioids			
Tramadol capsules	50-100mg *100–200mg*	400mg daily *200mg twice daily*	50-100mg standard release 3 to 4 times a day *Price variation in brands in primary care.* N.B. Increased risk of CNS toxicity when tramadol given with Selective Serotonin Re-uptake inhibitor (SSRI) or tricyclic.
Morphine	20-120mg	200mg daily	Initially 5-20mg every 4 hours. Increase dose weekly as required. When the pain is controlled and the patient's 24-hour morphine requirement is established, the daily dose can be given as a modified-release preparation.
Step 6 REFER TO SPECIALIST PAIN CLINICIAN			

Approved by APC: Sept 2014. Updated August 2017 (following pregabalin protected patent removal); Expiry: Sept 2017

Evidence and notes

Tricyclic Antidepressants

- All are unlicensed but have been used for many years.[2]
- They are considered an effective treatment for neuropathic pain and have a NNT of 3.6 (95% CI 3-4.5)[7]
- Nortriptyline may be better tolerated than amitriptyline.[1]
- Can cause drowsiness, caution with driving *etc.*
- Adverse effects often improve with time.
- Taking the drug at 7 - 8pm can help avoid residual effects the following morning.

Anticonvulsants

- It is important to explain to the patient that anticonvulsants can be prescribed to improve pain.
- They may take time to act.
- Can cause drowsiness, caution with driving and operating machinery; adverse effects often improve with time.
- Ensure patients have adequate dose titration with gabapentin before trying the next step.
- Carbamazepine has an NNT of 1.9 (CI 1.6-2.5) for PHN and 1.7 (CI 1.3 -2.2) for trigeminal neuralgia.[8]
- Gabapentin at a dose of 1200mg daily or greater has an NNT of 7.5 (CI 5.2-14) for PHN and 5.8 (CI 4.3-9.0) for diabetic neuropathy, for at least 50% pain relief.[9]
- There is no evidence that gabapentin is superior to carbamazepine.[9]

Pregabalin

- NNT of 5 for >50% pain relief in PHN, diabetic neuropathy.[2]
- Pregabalin is a gabapentinoid and believed to have the same mechanism of action as gabapentin.[2]
- Continue use only if beneficial pain relief is demonstrated following a 1-2 month trial.
- Adverse effects are dose dependent and a TDD above 300mg may lead to more withdrawals due to intolerance.
- Doses should be titrated up through the 7 different strengths available rather than in 25mg increments. Combinations of different strength products should be avoided.
- The most commonly reported adverse reactions are dizziness and somnolence
- Weight gain is a potential side effect and the manufacturers advise that adjustment of hypoglycaemic medication in diabetic patients if they gain weight.
- Scottish Medicines Consortium (SMC) accept the restricted use of pregabalin in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments for peripheral neuropathic pain.[10]
- **Misuse of pregabalin (and gabapentin) has been highlighted by the Local Intelligence Network. Pregabalin has value as a street drug known as 'Bud' and is a highly sought medication because of its use in enhancing the effects of opiates and the inherent abuse potential. GPs are asked to be aware of patients asking for additional supplies, rapid dose escalation or where the indication is not clear. Advice for prescribers on the risk of misuse of pregabalin and gabapentin is available from Public Health England.[11]**

Opioids

- Opioids alone may control a third of cancer-related neuropathic pains, and partially control a further third.
- The evidence for the short term use of opioids is equivocal but in longer term studies they show a significant efficacy over placebo.[12] The Cochrane review points out however that their long term safety needs to be established. It also points out the common but non life threatening side effects of nausea, dizziness and drowsiness.[12]
- A Cochrane review of tramadol found evidence that it is effective in the treatment of neuropathic pain with an NNT of 3.8 (CI 2.8-6.3) for 50% pain relief.[13] However it is associated with side effects including constipation, nausea, sedation and dry mouth. These resulted in 1 in 8 people in the trials included in the review dropping out [NNH 8.3 (CI 5.6-17)].

References

1. Joint Formulary Committee. British National Formulary No 66. *BMJ Group and RPSGB*, London; 2013.
2. Regional Drug and Therapeutics Centre (RDTC). Drug Update Neuropathic Pain; September 2007.
3. A. Topol. Pregabalin – for neuropathic pain (update). *London New Drugs Group*: APC/DTC Briefing Document; February 2005.
4. M. Watson *et al*. Oxford Handbook of Palliative Care, 2nd Edition. *Oxford University Press*, Oxford; March 2009.
5. Twycross and A. Wilcock. Palliative Care Formulary, 4th Edition. Palliativedrugs.com Ltd., Sept 2011.
6. Duloxetine (Cymbalta®) for the treatment of diabetic peripheral neuropathic pain. *Midlands Therapeutic Review and Advisory Committee* (MTRAC). October 2009.
7. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007, Issue 4.
8. Wiffen PJ *et al.* Carbamazepine for acute and chronic pain in adults (Review). *Cochrane Database of Systematic Reviews* 2011, Issue 1.
9. Moore RA *et al*. Gabapentin for chronic neuropathic pain and fibromyalgia in adults (Review). *Cochrane Database of Systematic Reviews* 2011, Issue 3.
10. Scottish Medicines Consortium. Pregabalin capsules; 157/05, May 2009.
11. Public Health England. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin; December 2014.
12. McNicol ED *et al*. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8.
13. Hollingshead J *et al*. Tramadol for neuropathic pain (review). *Cochrane Database of Systematic Reviews* 2009, Issue 2.

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14. NICE Clinical Guideline 173. November 2013 (Updated February 2017). Neuropathic Pain: The pharmacological management of neuropathic pain in adults in non-specialist settings.

NICE Clinical Guideline 173 on the Pharmacological Management of Neuropathic Pain in Adults in Non-Specialist Settings[14] has been reviewed fully by the APC in the making of this guideline in terms of clinical and cost effectiveness, safety, affordability and equity.

Appendix 1: Treatment pathway for patients presenting with shingles.

Antiviral therapy* (acyclovir 800mg 5 times daily for 7 days) should be considered in adults >50 years [Post-herpetic neuralgia (PHN) rare if <50 years] who present within 72 hours of symptoms, and adults of any age who:

- Are immunosuppressed or undergoing chemotherapy
- Have ophthalmic involvement (requires urgent referral to ophthalmology)
- Have shingles affecting area other than the torso
- Have moderate to severe pain
- Have moderate to severe rash
- Have Ramsay Hunt syndrome
- have atopic eczema
- Have contacts with very young infants, immunocompromised people or pregnant women.

**In line with Worcestershire Guidelines for Primary Care Antimicrobial Prescribing*

Predictive factors for PHN [shooting/burning pain in same area as the rash and/or allodynia (pain following an innocuous stimulus)] are: elderly; extensive rash within 72 hours; severe/prolonged prodromal pain.