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Management of Neuropathic Pain

WHAT IS NEUROPATHIC PAIN?

Neuropathic pain is pain that develops as a result of damage to, or dysfunction of, the nervous system. It may arise from a heterogeneous group of disorders that affect the peripheral and central nervous systems. Examples include post-herpetic neuralgia, diabetic neuropathy and trigeminal neuralgia.

Neuropathic pain is most commonly described as burning, stabbing or shooting pain. Patients often have altered pain sensation with allodynia (pain from an innocuous stimulus e.g. cotton wool) and hyperalgesia (more pain than expected from a stimulus such as pinprick).

TREATMENT OF NEUROPATHIC PAIN

Neuropathic pain is often difficult to treat because it is resistant to many medications and the adverse effects associated with effective medication can often limit their use. Neuropathic pain is less likely to be helped by traditional analgesia – it does not respond well to simple analgesics including non-steroidal anti-inflammatory drugs but opioids may be of benefit in some patients.

Anti-depressants e.g. amitriptyline and anticonvulsant drugs e.g. gabapentin and pregabalin are used in the treatment of neuropathic pain. However many patients have mixed pain syndromes, with nociceptive and neuropathic features. In this instance, standard analgesia, following the WHO Analgesic Ladder, should be prescribed with adjuvant therapies such as an antidepressant or anticonvulsant.

NHS Tayside has guidance available for the treatment of neuropathic pain. This can be accessed through the Pain guidance notes within the Central Nervous System Guidelines of the [Tayside Area Formulary](#). The algorithm summarising this guidance is shown on page 4.

The **first line** adjuvant therapy for neuropathic pain is either amitriptyline or gabapentin. Individual patient circumstances should be considered when selecting which to prescribe. Gabapentin **capsules** are more cost-effective than gabapentin tablets.

Amitriptyline (Tricyclic antidepressant)

Consider first line choice if:

- poor sleep
- poor compliance with medication (once-daily dosing)
- polypharmacy (large number of tablets per day)

Tricyclic antidepressants are not licensed for treatment of neuropathic pain; however there is a large evidence and practice base to support their use and this is an established indication.

- The starting dose of amitriptyline is 10mg at night.
- This should be continued for 2 weeks then increased to 20mg at night.
- This should be continued for 6 weeks then evaluated for response. It may take 2 to 6 weeks for it to be effective.
- The dose can then be increased gradually according to tolerance and the patient's needs. Doses above 50mg are seldom required.
- Particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
- Patients can be provided with a leaflet on taking amitriptyline for pain. [Click here](#)

Clomipramine or nortriptyline are suitable alternatives to amitriptyline.

Gabapentin (Anticonvulsant)

Consider first line choice if:

- contraindication to tricyclic antidepressant
- night sedation would be problematic (e.g. main carer, shift worker)
- poor drug tolerance (gabapentin is often better tolerated than amitriptyline)

TREATMENT OF NEUROPATHIC PAIN (continued....)

The anticonvulsant of choice is gabapentin, which is licensed for the treatment of neuropathic pain. Gabapentin should be titrated slowly according to tolerance and the patient's needs.

- The maximum starting dose is 300mg in the evening.
- Slower titration, starting at a dose of 100mg in the evening is recommended in elderly patients, in renal impairment and for drug sensitive patients.
- The dose must be reduced in renal impairment based upon individualised creatinine clearance. Information about dosing of gabapentin in renal impairment and/or those undergoing haemodialysis can be found in the Summary of Product Characteristics (SPC) for the particular product, available from the [electronic Medicines Compendium \(eMC\) website](#).
- Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
- Detailed advice for the titration of gabapentin can be found in the [Management of Neuropathic Pain](#) guidance within the Central Nervous System Guidelines of the Tayside Area Formulary. A patient information leaflet for gabapentin is also available which details the usual and slower initiation regimen.

[Click here](#)

Evaluation of effectiveness should not start before the patient has titrated the dose up to 600mg three times a day. If there is no improvement after 8 weeks of reaching the maximum tolerated therapeutic dose, alternative treatment should be considered. Gabapentin should not be stopped abruptly and should be reduced gradually over a **minimum** of 1 week, depending on dose and duration of treatment.

Combination therapy

If symptoms persist with either amitriptyline or gabapentin alone, combination therapy of amitriptyline and gabapentin should be considered.

Pregabalin (Anticonvulsant)

Within NHS Tayside pregabalin may be used in patients who have not achieved adequate pain relief from, or did not tolerate, first and second line drug treatments. Pregabalin can be used in combination with a tricyclic anti-depressant but should not be co-prescribed with gabapentin.

Pregabalin is licensed for neuropathic pain.

- The maximum starting dose is 75mg morning and night.

- The dose must be reduced in renal impairment based upon individualised creatinine clearance. Information about dosing of pregabalin in renal impairment can be found in the [Summary of Product Characteristics \(SPC\) for pregabalin \(Lyrica®\)](#).
- The dose may also require to be reduced in drug sensitive or elderly patients. **Patients who have previously been intolerant of other anticonvulsant therapy should start on a reduced dose of pregabalin.** A suitable starting dose may be 25mg morning and night.
- It should be titrated slowly according to response and tolerability.
- Detailed advice for the titration of pregabalin can be found in the [Management of Neuropathic Pain](#) guidance within the Central Nervous System Guidelines of the Tayside Area Formulary
- Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
- Twice daily dosing is more cost-effective than three times a day dosing.

Pregabalin should be discontinued if the patient has not shown sufficient benefit within 8 weeks of reaching the maximum tolerated therapeutic dose and the patient should be referred to the Pain Clinic. Pregabalin should not be stopped abruptly but should be reduced gradually over a **minimum** of 1 week, depending on dose and duration of treatment.

Conversion of Gabapentin to Pregabalin

As switching from gabapentin to pregabalin has not been investigated in clinical studies, there is limited information available. Advice in the [Summary of Product Characteristics \(SPC\) for gabapentin 300mg capsules](#) (Winthrop Pharmaceuticals UK Ltd), recommends that when it is necessary to discontinue or substitute gabapentin with an alternative medication this should be done gradually over a minimum of 1 week. The [SPC for pregabalin capsules \(Lyrica®\)](#) does not make a recommendation on initiating pregabalin subsequent to gabapentin or any other medicines.

The pain service has advised the following direct switch approach would be reasonable:

(continued over.....)

TREATMENT OF NEUROPATHIC PAIN (continued....)

- replace gabapentin 300mg three times a day with pregabalin 100mg twice a day
- replace gabapentin 600mg three times a day with pregabalin 200mg twice a day
- replace gabapentin 900mg three times a day with pregabalin 200mg twice a day

(Note: switch to pregabalin 200mg twice a day is recommended from both 600mg and 900mg three times a day of gabapentin).

The dose of pregabalin can be further increased depending on response and tolerability to a maximum dose of 300mg twice a day or 200mg three times a day.

Patient factors such as response to gabapentin and tolerability of previous drugs (including gabapentin) should be considered. For instance if gabapentin had to be increased slowly due to adverse effects, this may also be required for pregabalin.

Alternative Treatments

- Other anti-epileptic medication such as sodium valproate and carbamazepine can be tried if the above have failed but their use is often limited by side effects.
- Drugs used “off-label” or outwith SMC advice, may be indicated in some patients who have not responded to standard treatment – prescribing would be by the Pain Clinic via the local [Policy on the Prescribing of Medicines for Exceptional Use](#).

LOCAL INTERPRETATION OF NICE GUIDANCE

The National Institute for Health and Clinical Excellence (NICE) recently published a guideline for the pharmacological management of neuropathic pain in adults in non-specialist settings.

NICE clinical guidelines such as the guideline for the pharmacological management of neuropathic pain, do not apply in Scotland.

The Scottish Medicines Consortium (SMC) issues advice on new drugs and their position in therapy within NHS Scotland.

The SMC has accepted pregabalin for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in adults. It is restricted for use in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments for peripheral neuropathic pain.

The NHS Tayside guidance and algorithm for the treatment of neuropathic pain reflects the SMC advice and should be followed for the treatment of neuropathic pain within NHS Tayside.

This bulletin was produced by Karen Brown, Specialist Clinical Pharmacist, Specialist Services and the NHS Tayside Pain Service.

Algorithm for Neuropathic Pain

Diagnosis

- Common pain descriptors: burning, tingling, shooting or excessive sensitivity
- Sensory examination: Allodynia (pain from an innocuous stimulus e.g. cotton wool), hyperalgesia (more pain than expected from a stimulus such as pinprick)
- Note: many patients have mixed pain syndromes, with nociceptive and neuropathic features, use this algorithm along with standard analgesics.

Holistic Assessment

Consider the following when selecting antidepressant or anticonvulsant first – line therapy for neuropathic pain.

- Work/shift patterns
- Poor sleep
- Previous failed treatments
- Responsibilities e.g. main carer/dependants/return to work issues.

Tricyclic antidepressant – Amitriptyline

- Titrate from a low dose (10 – 20mg)
- Titrate for at least 4 weeks
- See management notes

Consider first line choice if:

- Poor sleep
- Poor compliance with medication (once daily dosage)
- Polypharmacy specifically large numbers of tablets/ day

Anticonvulsant - Gabapentin

- Titrate according to dosing regime
- Trial for at least 4 weeks
 - See management notes

Consider if:

- Contraindication to tricyclic antidepressant
- Night sedation would be problematic (e.g. main carer, shift worker)
- Poor drug tolerance, gabapentin is often better tolerated than amitriptyline.

Persisting Symptoms

Persisting Symptoms

Many patients may require a COMBINATION of tricyclic and anticonvulsant therapy. See management notes.

Persisting Symptoms

Anticonvulsant – Pregabalin

- Use third line if not achieved adequate pain relief or not tolerated first and second line treatments with tricyclic antidepressant +/- gabapentin
- Can be used in combination with a tricyclic antidepressant
- **Not** to be co-prescribed with gabapentin
- Titrate slowly according to dosing regime
- See management notes

Pregabalin should be stopped if a patient has not shown sufficient benefit within 8 weeks of reaching the maximum tolerated therapeutic dose of pregabalin and referred to the PAIN CLINIC.

**REFER to
PAIN CLINIC**

Consider the following options when referring patients to the Pain Clinic:

- If no improvement in symptoms, gradually withdraw pregabalin over a minimum period of a week. Do not stop abruptly.
- If some benefit achieved then continue until reviewed by Pain clinic.

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