CLINICAL GUIDELINE

Chronic Non Malignant Neuropathic Pain

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Contents

What is neuropathic pain?

It is: “Pain caused by a lesion or disease of the somatosensory nervous system.”

Signs and symptoms

- Burning
- Electric shocks
- Numbness
- Tingling
- Shooting/stabbing

Consider possibility of serious underlying pathology and refer for investigation as indicated.

NEUROPATHIC PAIN ASSESSMENT

Many Neuropathic Pain scoring tools e.g. LANSS are available for primary care use. The IASP criteria of “Possible”, “Probable” and “Definite” NP might be easier to use.

This classifies the pain depending on whether the patient describes pain in an anatomically plausible distribution of a nerve, has corresponding findings on examination in that same distribution, and then a confirmatory diagnostic test to respectively satisfy those three definitions in sequence. First line treatment can be initiated for possible neuropathic pain. If possible criteria is not satisfied it is unlikely to be neuropathic pain.

Example: for radicular leg pain

Possible=pain in a specific dermatome

Probable= signs in that dermatome e.g. straight leg raise

Definite= an MRI showing nerve impingement at that level

Examples of Neuropathic Pain

- Post herpetic neuralgia (PHN)
- Peripheral neuropathy (e.g. diabetic, alcohol related, cancer/chemotherapy related)
- Trigeminal neuralgia (TN)
- Nerve root pain
- Post surgical
- Phantom limb pain

Complex Regional Pain Syndrome (CRPS) Info

- “CRPS is a neuropathic pain condition that occurs in a limb or body region and should be considered when there is a disproportionate pain response to the initial injury and a mixture of sensory, vasomotor, sudomotor or trophic changes.”
- Link to 2018 Tx pathway statement (RCPE) https://www.rcplondon.ac.uk/guidelines-policy/complex-regional-pain-syndrome-adults

Prescribing drugs for neuropathic pain

Before prescribing

1. Establish diagnosis and explain implications and chronicity to patient, and importance of compliance with treatment.
2. Assess pain and function, and if it is helpful use e.g. Brief Pain Inventory to aid, taking into account psychosocial factors.
3. Consider non-medication therapies physical and psychological therapies along with lifestyle changes if relevant. GG&C Health and Wellbeing Directory has a wide variety of resources.
4. Consider potential side effects/interaction from these drugs.
5. Assess risk of abuse/dependence if considering gabapentin/pregabalin (Class C substances; see Appendix 5).

Initiating a trial

Talk to patient about treatment plan

a. Choice of drug.
b. Set realistic goals: 30% reduction in pain or 30% improvement in function.
c. Discuss benefits and side effects (and that side effects may improve with time).
d. Discuss trial period including dose titration and the titration process.
e. Start low and go slow.
f. Discuss when this medication should be discontinued.
g. Plan review appointment – review 2-4 weeks after initiation, then allow 4 weeks of maximum tolerated dose before effects judged.
h. If one drug is not effective, wean and discontinue and choose alternative option. If it is partially effective, consider adding a second drug rather than substituting.
i. Check that patient understands.

Should treatment continue?

Arrange regular review of pain and function and side effects

a. For all patients who are benefiting, review the need to continue treatment with periodic trial of reduction every 6 -12 months; agree on flare-up management (Appendix 4).
b. For all patients who are not benefiting, wean and discontinue medication.
c. For patients who are at risk of abusing medication, consider increased supervision e.g. instalment dispensing.
d. For all patients who are abusing medication, wean and discontinue the medication.

Cannabinoid statement

- “There is insufficient clinical and research evidence to support the use of cannabinoid drugs in the treatment of neuropathic pain. The use of medicinal cannabis for chronic pain conditions is not recommended at this time.”

Step 1 Treatments – Amitriptyline and/or Gabapentin

There is stepwise guidance on the chronic pain website www.paindata.org

There is no strong evidence to choose one Step 1 drug over the other; this depends on patient factors and prescriber experience. If the first agent chosen is not effective, then a drug from the alternative class may be used **either** as sole agent or in combination.

- It is paramount to explain to patients with neuropathic pain prior to initiating any drug that a realistic treatment aim would be a 30% reduction in pain rather than complete cure.
- Regular review of symptoms and side effects should be conducted on all neuropathic agents, particularly with Gabapentin and Pregabalin given the abuse potential and scheduling of gabapentinoids as controlled substances.
- Periodic trial reduction should also be considered with review at least every 6 – 12 months.

Amitriptyline (PIL)

- Imipramine or nortriptyline can be prescribed instead if sedation or hypotension is a problem. Both have the same dose and titration schedule to amitriptyline.
- Use most cost effective product.
- Neuropathic pain is an unlicensed although recognised indication for all three drugs.

In frail and elderly:
Start with 10mg in frail, elderly and increase in 10mg increments every 3-7 days to maximum of 50mg per day.

In younger patients:
Start with 10-25mg and increase in steps of 25mg every 3-7 days to 100mg maximum per day

Managing side effects:
To minimise morning sedation or hangover effects take at night or take medication 12hrs before the patient scheduled wake up time.
Nortriptyline may be less sedating than amitriptyline; consider prior to amitriptyline in eldery patients.

Dose adjustment/caution:
Use lower dose if the patient is already on an alternative antidepressant e.g. Amitriptyline 25mg per day.
Caution should be exercised in patients taking other serotonergic drugs such as SSRI's and Tramadol for the potential of Serotonin excess and Serotonin Syndrome.

When to stop trial:
If no benefit at 6-8 weeks of maximum tolerated dose.

Ongoing review:
Review the need to continue treatment with periodic trial of reduction every 6-12months. Advice on weaning is in the drug patient information leaflets and refer to section on 'Prescribing drugs for neuropathic pain'.

Gabapentin (PIL)

In adults:
Start at 300mg at night and increase in 300mg increments at weekly intervals aiming for a dose of between 1200mg and 1800mg daily. Doses of up to 3600mg in 24 hours have been used, where beneficial and tolerated.

In frail patients:
Start with 100mg at night in frail, elderly and increase by the same amount weekly. Titrate to effect, but not above 1800mg per day

In renal failure:
Use lower dose and refer to BNF. Appendix 2.

When to stop trial:
If no benefit at 6-8 weeks of maximum tolerated dose.

Ongoing review:
Review the need to continue treatment with periodic trial of reduction every 6-12months and refer to section on 'Prescribing drugs for neuropathic pain'.

Carbamazepine – (PIL) can be used as first line treatment in classical Trigeminal Neuralgia (TN) – see below.

Step 2 Treatment

Pregabalin (PIL) is an alternative in patients who have found no benefit from, or have not tolerated conventional first or second line agents(as per Scottish Medicines Consortium (SMC) restriction) i.e. gabapentin or amitriptyline.

In adults:
Start at dose of 75mg twice a day; Titrate up to a maximum dose of 300mg twice a day using the most cost effective preparation. (One capsule twice daily is always the most cost effective regimen).

In frail/elderly:
75mg once daily ; Titrate up to a maximum dose of 300mg twice a day using the most cost effective preparation. (One capsule twice daily is always the most cost effective regimen).

When to stop trial:
If no benefit at 6-8 weeks of maximum tolerated dose.

Ongoing review:
Review the need to continue treatment with periodic trial of reduction every 6-12months and refer to section on 'Prescribing drugs for neuropathic pain'.

Pregabalin and risks in pregnancy

There are risks to unborn babies who are exposed to pregabalin:

- Taking pregabalin during pregnancy may slightly increase the chance of physical birth abnormalities in the baby; the overall risk is low.
- **Don't stop taking pregabalin without discussing it with your prescriber; they are the best person to talk to about your individual situation.**
- **If you are taking pregabalin you should continue to use effective contraception* during treatment.**
- **If you are currently planning to have a baby, it is important to discuss your treatment options with your healthcare professional before you stop using effective contraception.**
- If you think you may be pregnant or need advice while taking pregabalin, talk to the healthcare professional who prescribes pregabalin for you.

For more information on the above, please use the link below:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1070488/Pregabalin-PSL-April_2022_V2.pdf

*Examples of effective (E) and highly effective (HE) contraception include:

- (E) Subcutaneous, or intramuscular depot medroxyprogesterone acetate (DMPA),
- (E) Combined hormonal contraceptive pills, patches or vaginal ring.
- (E) Progesterone only pills
- (HE) Copper intrauterine device
- (HE) Levonorgestrel releasing intrauterine system

For full table:
https://assets.publishing.service.gov.uk/media/5c936a4840f0b633f5bfd895/pregnancy_testing_and_contraception_table_for_medicines_with_teratogenic_potential_final.pdf

SWITCHING FROM GABAPENTIN TO PREGABALIN OR VICE VERSA

There are different ways of switching between pregabalin and gabapentin. Below is a method for direct switching between the two drugs, which does not involve cross-titration.

If considering switching a patient from Gabapentin to Pregabalin, or vice-versa, the following equivalence is suggested with Pregabalin roughly six times more potent than Gabapentin:

Total daily dose of Gabapentin	**Total daily dose of Pregabalin**
0-900mg	**150mg**
901-1500mg	**225mg**
1501-2100mg	**300mg**
2101-2700mg	**450mg**
Above 2700mg	**600mg**

One drug should be discontinued after a final evening dose, with the new drug commenced the following morning.

Pregabalin and Gabapentin risk of abuse and dependence

Since the last guideline was produced the potential for abuse and dependence has been recognised in patients being treated with Gabapentin and Pregabalin.

This has resulted in these medications being controlled under the Misuse of Drugs act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3.

1. Before prescribing patients should be assessed for risk of abuse/dependence
2. Patients already taking Pregabalin or Gabapentin should be observed for signs of abuse/dependence including drug seeking behaviour, dose escalation or development of tolerance.
3. Patients should understand the risks associated with these medications which also include potentially fatal interactions with other sedative medication including opioids and alcohol.
4. Prescribers should report any adverse reactions to these medications on a Yellow Card including cases of abuse or dependence.

These medications are not subject to safe custody requirements, but it is illegal to be in possession of either Pregabalin or Gabapentin without a current prescription.

Step 3 Treatment

Duloxetine (PIL) –
This has been accepted by the SMC for painful diabetic neuropathy and is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as a second or third therapy. Duloxetine is licensed in the UK at a maximum dose of 120mg a day for the treatment of diabetic peripheral neuropathic pain. However most sources recommend a dose of 60mg a day, as there is no evidence that doses higher than 60 mg confer additional significant benefit.

- Start with 30mg per day for two weeks and titrate up to a max of 60mg per day.
- Maximum dose to be given in divided doses.

Side effect:
In contrast to gabapentinoids, the side effect profile is more one of appetite suppression than weight gain commonly seen with the latter. This may be beneficially harnessed in some patients e.g. overweight diabetics.

If patient is benefiting from the medication but experiencing nausea, consider concurrent prescription of a formulary-approved anti-emetic.

When to stop trial

- Use for an 8 week trial, allowing 4 weeks at max tolerated dose, discontinue if inadequate response.
- If to be discontinued dose should be reduced over 1-2 weeks to minimise withdrawal effects.

Ongoing review:
Review the need to continue treatment with periodic trial of reduction every 3 months and refer to section on 'Prescribing drugs for neuropathic pain'.

Cautions/ MHRA warnings

MHRA warn of a risk of suicidal ideation and request a review every 3 months for signs of depression/suicidal ideation.

Duloxetine can cause hypertensive crisis so if patient already has hypertension and/or cardiac disease the BP monitoring should be performed especially during the first month and duloxetine should be avoided if patient has uncontrolled hypertension.

Carbamazepine (can be used as first line treatment for Trigeminal Neuralgia)

Dosing:
Initial dose of 100-200mg daily, increasing slowly in increments of 100-200mg at weekly intervals
Usual maintenance dose range 600-1200mg in 24 hours
Maximum dose of 1600mg per day.

Monitoring:

Pre-treatment blood testing for leucopaenia (10% of patients), liver derangement and hyponatraemia is required. Repeat testing should be carried out two weeks after initiation, then monthly intervals for the first three months and based on clinical need thereafter. Prescribers should have an awareness of the potential for suicidal ideation which has been described (frequency unknown)

When to stop trial:
If no benefit at 6-8 weeks of maximum tolerated dose.

Ongoing review:
Review the need to continue treatment with periodic trial of reduction every 6-12months

Other treatments- only use if Steps 1-3 have failed

Topical treatments

Lidocaine 5% Medicated Plasters (PIL)

When to use:

This is restricted to patients who are intolerant of first line therapies for post-herpetic neuralgia or where these therapies have been ineffective. Use for other indications remains non-Formulary.

How to use:

The lidocaine plaster should be worn once daily for 12 hours on and 12 hours off.

Use the least number of plasters required for effective treatment.

The plasters may be cut into smaller sizes with scissors if required in order to minimise wastage.

In total, not more than three plasters should be used at the same time.

When to stop trial:
Treatment should be re-evaluated 2 – 4 weeks after initiation - discontinued if they do not demonstrate a 30% improvement in baseline pain scores and/or function

Ongoing review:
Studies have shown that the number of plasters can decrease over time. Patients should be reviewed at 6-12 monthly intervals to see if amount of plaster can be reduced or if the plaster-free period can be extended.

Capsaicin 0.075% cream (PIL) can be used for people with localised neuropathic pain who wish to avoid, or cannot tolerate, oral treatments. Evidence of efficacy is poor, but side effects are minimal. Period trial of cessations should be considered.

Opioids

There is a limited role for opioids in chronic non-malignant pain

Tramadol and potent Opioids – Follow local NHS GG&C Opioid guidelines

Treatment of Post Herpetic Neuralgia

Offer self-management advice:

- Wear loose clothing or cotton fabrics, as these will usually cause the least irritation
- Consider protecting sensitive areas by applying a protective layer (such as cling film or a plastic wound dressing).
- Consider frequent application of cold packs, unless this causes pain (allodynia).

Offer analgesia to manage pain:

- Offer paracetamol with or without codeine if the person's pain is mild or moderate, and there are no contraindications
- If pain remains uncontrolled, treat with standard oral anti-neuropathic medication as per Steps 1-3.
- Consider prescribing capsaicin cream if pain is mild or as an adjunct to oral therapy if pain is severe
- Consider lidocaine 5% plasters. This is restricted to patients who are intolerant of first line therapies for post-herpetic neuralgia or where these therapies have been ineffective. Use for other indications remains non-Formulary.

Consider referral to pain services if pain is unresponsive to treatment or significantly limits their participation in daily activities.

Treatment of Trigeminal Neuralgia

Use Carbamazepine 1st line

Dosing:
Initial dose of 100-200mg daily, increasing slowly in increments of 100-200mg at weekly intervals
Usual maintenance dose range 600-1200mg in 24 hours
Maximum dose of 1600mg per day.

Monitoring:
Pre-treatment blood testing FBC, U&Es and LFTs for leucopenia (10% of patients), liver derangement and hyponatraemia is required. Repeat testing should be carried out two weeks after initiation, then monthly intervals for the first three months and based on clinical need thereafter. Frodo .Prescribers should have an awareness of the potential for suicidal ideation which has been described (frequency unknown).

When to stop trial: if no benefit at 6-8 weeks of maximum tolerated dose.

Ongoing review: Review the need to continue treatment with periodic trial of reduction every 6-12months.

Caution: Not advised for use in moderate to severe renal impairment.

If there is inadequate response, treatment is not tolerated or in the presence of red flag symptoms consider early referral for specialist advice, for example neurosurgery.

When to refer

Consider referral to pain services and/or other condition specific specialists if the person has severe pain or their pain significantly limits their lifestyle, daily activities (including sleep disturbances and participation), or their underlying health condition has deteriorated.

The patient should also be ready and willing to engage with multi-disciplinary approach to managing their pain.

Follow referral criteria in Appendix 3 and the Chronic Pain Primary Care Guidelines

Appendix 1

NNT's

A recent meta-analysis of the pharmacotherapy for neuropathic pain in adults showed that outcomes were relatively modest. Trials were included with treatments lasting longer than 3 weeks' duration and achieved 50% pain relief with the following Numbers Needed to Treat (NNT) and Numbers Needed to Harm (NNH).[1] The table is based on meta-analysis from Finnerup NB et al.

Drug	**Number Needed to Treat**	**Number Needed to Harm**	**Quality of final evidence**
Tricyclic antidepressants (TCA)	3.6 (95% CI 3.0-4.4)	13·4 (9·3–24·4)	Moderate
Serotonin-noradrenaline re-uptake inhibitor (SNRI) antidepressants duloxetine and venlafaxine	6.4 (95% CI 5.2-8.4)	11·8 (9·5–15·2)	High
Pregabalin	7.7 (95% CI 6.5-9.4)	13·9 (11·6–17·4)	High
Gabapentin	7.2(95% CI 5.0-8.3)	25·6 (15·3–78·6) and 31.9 for ER preps	High
Topical lidocaine	No information	No information	Low
Capsacin 8%	10·6 (7·4–19)	No information	High

Results of this meta-analysis showed that the efficacy of systemic drug treatments was generally not dependent on the aetiology of the underlying disorder. The authors of the meta-analysis propose first line use for TCAs, SNRIs, pregabalin and gabapentin in neuropathic pain; a weak recommendation for lidocaine patches, capsaicin patches as second line; and a weak recommendation for strong opioids (particularly oxycodone and morphine) as third line.

[1] Finnerup NB et al 2015. Pharmacotherapy for neuropathic pain in adults a systematic review and meta-analysis

Appendix 2

Renal impairment

NB – Patients with renal impairment should have their dose of gabapentin or pregabalin reduced per BNF recommendation below.

eGFR (mLs per minute per 1.73m^2	**Total daily gabapentin dose mg (to be administered in three divided doses)**
50-79	600-1800
30-49	300-900
15-29	150mg- 600mg (150mg daily dose to be given as 300mg in three divided doses on alternate days)
<15[a]	150mg- 300mg (150mg daily dose to be given as 300mg in three divided doses on alternate days)

a. For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

eGFR (mLs per minute per 1.73m^2	**Total daily pregabalin dose**	
	Starting daily dose	**Maximum daily dose**
30-60	75mg	300mg (in two or three divided doses)
15-30	25-50mg	150mg (in two divided doses or as a single daily dose)
<15	25mg	75mg (as a single daily dose)

Amitriptyline-No dose change suggested in renal impairment

Duloxetine-No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min).Duloxetine **must not be used** in patients with severe renal impairment (creatinine clearance <30 ml/min)

Lidocaine plasters- The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.

Appendix 3

Greater Glasgow and Clyde Pain Management Service Referral Criteria.

MISSION STATEMENT

'The pain management service provides multidisciplinary knowledge and skills to support people living with chronic non malignant pain. Chronic pain, for which there is often no cure, has a significant impact on quality of life. While we can and do optimise medical treatments, the overall aim of our approach is to inform and support people living with chronic pain to improve their quality of life. Those who adopt this supported self management approach are often more motivated and confident to manage their pain, and improve their quality of life'.

Referral criteria for patients with chronic non malignant pain

Patient resides within GG&C Health Board catchment area and is **18 years of age** or over. **

Pain has been present for more than 3 months with an adverse impact on quality of life.

Patient understands a cure may not be possible and that actively engaging in self management is more likely to improve quality of life than relying on medications alone.

If the patient requires further investigation or treatment, for their painful condition, please refer to the appropriate service before referring to the pain service (e.g. orthopaedics, rheumatology).

Current GG&C Chronic Pain Management guidelines should be followed prior to referral (This includes trials of appropriate medications and referral to MSK physiotherapy where appropriate).
(If in doubt please discuss with a pain consultant).

Exclusion criteria

Patients currently being actively investigated or awaiting treatment for the same condition by other specialties.

Patients with significant pre-existing mental health or addiction problems should be considered for referral to an appropriate service prior to referral to the pain service.

(If in doubt, please discuss with a pain consultant).

Re-referral

Patients should **not be re-referred** for the same pain problem if assessment and therapeutic options have been exhausted.

**(Patients aged 16 or 17 may be considered following discussion with a consultant).

(Patients residing in Argyle and Bute CHP catchment can be referred but may not be able to access the full GG&C service).

(If in doubt discuss prior to referral).

Appendix 4
Flare-up Management

Flare ups are common in people with chronic pain. Although flare ups are often distressing and frightening, they rarely indicate new damage.

• Advise patient to continue taking medication as prescribed.

• If short term changes to the patient's medication are required, then a management plan needs to be agreed between the patient and the healthcare provider and be adhered to. Return to normal medication when flare up has settled.

• Reduce exercise and normal activity, but maintaining some gentle activity as this is important.

• Suggest patient ask others to help during the flare up and gradually get back to usual levels of activity.

• Advise patient to learn deep breathing exercises and relaxation techniques. Check for negative thoughts and "catastrophic" thinking. Hot water bottles, heat packs, electric blankets, warm baths or Jacuzzis can sometimes help.

• Encourage the patient to eat regularly and have a few meals in the freezer that can be heated up.

• Distraction is often helpful – TV, reading, having someone to talk to etc.

• Return to normal activities and exercise when flare up has settled.

• Encourage patient to develop a flare up management plan that works for them. They should start the plan as soon as the flare up begins.

Appendix 5

Potential signs of misuse

***Appendix: risk of misuse assessment (including drug diversion). Not an exhaustive list.

1. History of substance misuse
2. Specific requests for prescription of Pregabalin or Gabapentin by patients
3. Request for Gabapentin or Pregabalin after release from the prison service
4. Repeated early prescription requests
5. Repeated reports of lost medication
6. Contact out of hours service for resupply of medication.
7. 'Doctor shopping' or online access for private prescription
8. Consider using the opioid risk tool (need link) to assess risk of problematic drug use
9. Consider PADT tool for monitoring of treatment and problematic drug use.