Management of Neuropathic Pain for Adults in Primary Care

SCOPE

This prescribing guideline is to assist primary care prescribers in treating patients with neuropathic pain BEFORE referral to specialist services.

CONTENTS

NEUROPATHIC PAIN TREATMENT PATHWAY 2
UNDERSTANDING NEUROPATHIC PAIN 3
HOW COMMON IS NEUROPATHIC PAIN? 3
RECOGNISING AND DIAGNOSING NEUROPATHIC PAIN 3
PREVENTION & EARLY MANAGEMENT OF NEUROPATHIC PAIN 4
MANAGEMENT 4
MANAGING EXPECTATION OF PHARMACOLOGICAL TREATMENTS 4
IMPROVING CONCORDANCE 5
REVIEW 5
SWITCHING TREATMENTS AND DOSE TAPERING 5
CAUTIONS WITH NEUROPATHIC PAIN THERAPIES 6
PHARMACOLOGICAL OPTIONS FOR MANAGEMENT OF NEUROPATHIC PAIN 6
PAIN MEDICINES AND DRIVING 8
RESOURCES FOR CLINICIANS AND PATIENTS 10
REFERENCES 11

NEUROPATHIC PAIN TREATMENT PATHWAY

PHARMACOLOGICAL MANAGEMENT

- See page 4 for information regarding realistic expectation of pharmacological management.
- Document baseline and agree with patient desired treatment outcomes before initiating therapies.
- Gabapentinoids, opioids or benzodiazepines are not recommended for the management of sciatica – if the 1st line treatment options are not effective refer to Pain Specialist.
- Ensure adequate doses are trialled for a long enough time before moving to the next step. Do not continue ineffective treatment i.e. use "short sequential trials "or "one medication at a time".
- See table on page 9 or refer to BNF and/or SPC for adverse effects and contraindications for specific medications.

NON-PHARMACOLOGICAL TREATMENT OPTIONS

- Address common psychological co-morbidities (e.g. anxiety/depression), consider referring/signposting to psychological therapies such as cognitive behavioural therapy *
- If sleep is disturbed discuss sleep restoration strategies *
- Physiotherapy
- Interventional approaches such as surgery

* Please see Clinicians Resources on page 10 for more information/options.

Refer patient to Specialist at any stage – where the diagnosis is in doubt or patient is not responding to treatment.

For **neuropathic pain** offer a choice of either:

1st LINE: AMITRIPTYLINE or DULOXETINE

2nd LINE: GABAPENTIN or PREGABALIN

Review 4 weeks after initiation or treatment change (to assess dosage titration, tolerability, adverse effects and suitability of chosen treatment), then at 3 months to assess effectiveness, and once stabilised review 6 monthly afterwards (esp. treatment with gabapentinoids).

If the initial treatment is not effective or tolerated, offer alternative 1st line option. Consider moving to 2nd line treatments only if initial therapy fails or is not tolerated. Consider switching between the 2nd line options if ineffective – see page 9 for guidance.

Has there been a significant decrease in pain AND satisfactory increase in physical function?

YES → Maintain on medication and dose that is working. Review regularly

NO → **STOP and try options below**

For **trigeminal neuralgia** offer CARBAMAZEPINE

Review at 6-8 weeks.

Has there been a significant decrease in pain AND satisfactory increase in physical function?

YES → Maintain on medication and dose that is working. Review regularly

NO → Consider referral to Specialist Pain Management Service

Other pharmacological treatment options to consider:

Nortriptyline – only use if amitriptyline effective but not tolerating side effects; off-label indication.

Tramadol – consider only if acute rescue therapy is needed.

Capsaicin 0.075% cream – for localised pain due to post herpetic neuralgia.

*Lidocaine 5% medicated plasters - for localised neuropathic pain due to post herpetic neuralgia (PHN). **Specialist Pain Team recommendation only – request via A&G (Amber 2).**

Has there been a significant decrease in pain AND satisfactory increase in physical function?

YES → Maintain on medication and dose that is working. Review regularly

NO → Consider referral to Specialist Pain Management Service

UNDERSTANDING NEUROPATHIC PAIN

Neuropathic pain is very different from inflammatory pain. Whilst nociceptive pain is produced by tissue damage neuropathic pain is caused by a lesion or disease affecting the somatosensory nervous system which can result from nerve damage caused by trauma or certain conditions.

HOW COMMON IS NEUROPATHIC PAIN?

- Neuropathic pain is a common condition affecting between 6% and 8% of the population.
- An average GP may have between 35 and 70 patients with neuropathic pain.
- Much neuropathic pain can be successfully managed within Primary Care.

RECOGNISING AND DIAGNOSING NEUROPATHIC PAIN

Common causes of neuropathic pain:

- Diabetes Mellitus (type 1 and 2)
- Shingles (Herpes Zoster)
- Trigeminal Neuralgia
- Post-Surgery e.g. post hernia repair
- Chronic spinal problems e.g. sciatica, neck pain, low back pain
- Underlying malignancy or other occult disease

Consider referring patient to specialist setting if:

- The patient is experiencing severe pain.
- Neuropathic pain is significantly limiting participation in daily activities (including self-care, general tasks and demands, interpersonal interactions and relationships, mobility, and sleeping).
- The underlying health condition that is causing neuropathic pain has deteriorated.

Emergency	Urgent	Non-Urgent
Cauda equina syndrome	Infection	Metabolic causes e.g. alcohol excess or vitamin deficiency
	Cancer	Phantom limb pain
	Trauma	Post-surgery
		Medication toxicity e.g. chemotherapy
		Idiopathic

Possible initial investigations if cause in doubt:

ESR, CRP, fasting glucose, glucose tolerance test, LFTs, FBC, Vitamin B_{12} & folate, U&Es, TFTs

Symptoms and signs of neuropathic pain:

- Can be spontaneous or evoked; continuous or intermittent.
- Is often worse at the end of the day.
- Can be exacerbated by heat, cold or external stimulation - even simply wearing clothes or bed sheets.

History:

- Listen to the person's pain story; this will help you to get a clear understanding of the person you are working with.
- Neuropathic pain may be characterized by unpleasant symptoms, such as: shooting or burning pain, altered sensation, sensations (e.g. pins and needles) that are very difficult to describe or numbness
- However, many pains, including pain arising from classically "non-neuropathic" conditions(e.g. osteoarthritis or cancer pain), can have neuropathic characteristics.
- Pain that is unresponsive to conventional analgesics (paracetamol, NSAIDs and weak opioids) may have neuropathic elements.

- Consider use of a validated questionnaire (e.g. S-LANSS or Pain Detect) to aid diagnosis of neuropathic pain.
- The Brief Pain Inventory is useful to assess pain intensity and the impact that the pain is having on daily living.

Sensory signs:

- Allodynia - pain produced by an innocuous stimulus e.g. touch, pressure, warmth
- Dysaesthesia - an unpleasant, abnormal sensation
- Hyperaesthesia - an increased sensitivity to touch
- Hyperalgesia - an increased response to a stimulus which is normally painful

Associated symptoms and signs:

- Reduced activity (65%)
- Poor sleep (60%)
- Depression (34%)
- Anxiety (25%)

PREVENTION & EARLY MANAGEMENT OF NEUROPATHIC PAIN

- **Diabetes** - Ensure optimal glycaemic control to minimise peripheral diabetic neuropathy.
- **Herpes zoster** - Neuropathic pain medicines given in the acute phase may reduce post-herpetic neuralgia but are unproven.

MANAGEMENT

- Management of neuropathic pain should use a holistic biopsychosocial model that alsoaddresses underlying psychological and social issues.
- If the diagnosis is uncertain consider early referral to a Specialist.

MANAGING EXPECTATION OF PHARMACOLOGICAL TREATMENTS

- It is essential that prescribers and patients have realistic expectations for treatment.
- Development of self-management skills (see Pain Toolkit) in combination with pharmacological treatment options is essential.
- Shared treatment outcomes (reduction in pain intensity or pain relief and functional outcomes) should be agreed and documented prior to initiation of treatments for neuropathic pain.
- Analgesics for neuropathic pain are unlikely to provide complete pain relief, however a successful trial should provide improvement in quality of life (i.e. improved lifestyle, daily activities including sleep, and participation) and noticeable reduction in pain intensity.
- Those patients who gain good pain relief often experience improvements in other physical and psychological domains (e.g. sleep, mood, quality of life).
- Effects are unlikely to be noticeable for up to two weeks after treatment initiation, but the maximum benefit may not be observed until 6-8 weeks. However, patients may experience side effects much sooner.
- Most side effects are relatively minor and will resolve if the patient is able to persist in taking the medication for several weeks.
- Reassessment of effectiveness by a gradual dose reduction at least once a year is advised to ensure that medicines are continuing to provide benefit.

IMPROVING CONCORDANCE

- Explain the reason and rationale for treatment choices.
- Explain commonly used medicines (e.g. antidepressants and antiepileptics) may be used for other conditions.
- Explain common side effects.
- Explain timescale expected for improvement and possible next step.
- Provide patient with an information leaflet about persistent pain and/or about medicines for neuropathic pain (please see resources for Clinicians).

REVIEW

- Patients should be followed closely to review diagnosis and ensure that the treatment is titrated to the response.
- At each review consider: the diagnosis, efficacy and tolerability of medication, and whether the dose adjustment is required.
- Once stabilised on treatment patients should be reviewed at least annually.
- The Brief Pain Inventory in appendix 1 is a useful tool to monitor the effect of management.
- Refer patient to specialist at any stage – where the diagnosis is in doubt or patient is not responding to treatment.

SWITCHING TREATMENTS AND DOSE TAPERING

- **Switching from amitriptyline or nortriptyline to duloxetine** requires cautious cross-tapering, usually undertaken over 2 to 4 weeks, starting with low dose duloxetine. The speed is determined by tolerability and should be tailored individually. An example cross-tapering regimen switching from amitriptyline to duloxetine is given in table below. Further information is available here.

	Pre-switch dose	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
Withdrawing amitriptyline / nortriptyline	75mg daily	50mg daily	40mg daily	25mg daily	10mg	Nil	Nil
Introducing duloxetine	Nil	30mg daily	30mg daily	60mg daily	60mg daily	60mg daily	60mg twice daily (if needed for pain relief)

- **Switching from duloxetine to amitriptyline** requires cautious cross-tapering, usually undertaken over 2 to 4 weeks, starting with low dose amitriptyline. The speed is determined by tolerability and should be tailored individually. Dose of duloxetine should be gradually reduced over a minimum of 1 to 2 weeks to reduce the risk of withdrawal reactions. Further information is available here.

- **When discontinuing duloxetine or reducing** the dose (for intolerance or ineffectiveness), gradually reduce the dose over a minimum of 1 to 2 weeks to reduce the risk of withdrawal reactions.

- Guidance on **switching between gabapentin and pregabalin** for neuropathic pain is provided by the Specialist Pharmacy Service and is available here.

CAUTIONS WITH NEUROPATHIC PAIN THERAPIES

- Use pain medicines with caution in patients who are frail, elderly or who have cardiac disease.
- Some of these drugs can potentially cause an increase in **falls risk**. Please see medicines and falls chart available here: https://www.nottsapc.nhs.uk/media/1501/falls_medicines_chart.pdf
- When initiating **amitriptyline** in patients over 65 years of age consider its anticholinergic properties, and the risks of **Anticholinergic Burden** i.e. increased cognitive impairment and mortality.
- Many medicines recommended are not licensed for the treatment of neuropathic pain.
- Opioids should be used on specialist recommendation only (except for tramadol when prescribed as acute rescue therapy) and as part of comprehensive management plan. Refer to the APC guidance on the use of opioids for persistent non-cancer pain and the Faculty of Pain Medicine Opioids Aware resource.
- Cases of **gabapentin and pregabalin** misuse are increasing. Both were reclassified as **Schedule 3 controlled drugs** due to concerns of **potential for abuse and dependence**.
- Use with caution for patients with a personal or family history of substance or alcohol misuse. Monitor all patients for any signs of abuse and dependence. See Drug Safety Alert for details.
- Gabapentin and pregabalin have been associated with risk of **respiratory depression** even without concomitant opioid medicines. Consider any necessary dose adjustments for patients at higher risk of respiratory depression, especially those:
  - with impaired respiratory function, respiratory or neurological disease, or renal impairment;
  - taking other CNS depressants including opiates;
  - over 65 years of age.

  Take special precautions for patients co-prescribed **opioid and pregabalin at doses exceeding 300mg a day**, as they are at an increased risk of death due to respiratory depression. See Drug Safety Alerts for details on gabapentin or pregabalin.
- Risk of **opioid related death** increased with **gabapentin and concomitant opioids** (ref: Gomes T at al).
- Gabapentin and pregabalin are commonly associated with inadvertent weight gain and patients should be informed this may worsen neuropathic pain (potentially due to increased pressure on nerves and inflammation).
- During the first trimester of pregnancy, the use of **pregabalin** may result in a slightly increased risk of major congenital malformations in the unborn child, compared to contemporaries. Counsel patients taking pregabalin on the potential risks to an unborn baby and the need to use **effective contraception** during treatment. See Drug Safety Alert for details.
- Carbamazepine use in pregnancy has been associated with an increased risk of major congenital malformations. See Drug Safety Alert for details. Counsel patients taking carbamazepine on the potential risks to an unborn baby and the need to use **effective contraception** during treatment.
- Other physical treatments (e.g. TENS, acupuncture, physiotherapy) may be beneficial.
- TENS is effective only while the machine is in use but may provide relief for short periods.

PHARMACOLOGICAL OPTIONS FOR MANAGEMENT OF NEUROPATHIC PAIN

Amitriptyline: licensed for neuropathic pain. The starting dose is 10-25mg at night, can be gradually increased by 10-25mg every 3-7 days up to the maximum dose of 75mg daily if tolerated (daily dose may be split). Try for 6-8 weeks with at least 2 weeks at the maximum tolerated dose, before deciding it is not effective. If not effective, gradually taper off and consider switching to alternative drug. Dosages higher than 75 mg a day could be considered in consultation with a specialist pain service. Consider the anticholinergic properties of amitriptyline and the Anticholinergic Burden in patients over the age of 65.

Duloxetine: licensed for the treatment of diabetic peripheral neuropathic pain but recommended by NICE for all neuropathic pain (except trigeminal neuralgia). The starting dose is 60mg once daily, can be increased up to the maximum of 120mg daily split in two doses. Try for 8 weeks, before deciding it is not effective. If not effective, gradually taper off over a minimum 1-2 weeks and consider alternative drug. Duloxetine belongs to Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) which have been associated with dose-related, often sustained increases in both systolic and diastolic blood pressure. Use with caution in patients with co-existing conditions that might be compromised by increases in blood pressure and heart rate.

Recommended monitoring:

- Baseline blood pressure (BP) measurement before starting treatment. If BP is raised (systolic >140mmHg or diastolic >90mmHg) this should be managed in line with current hypertension guidelines.
- Hypertension must be controlled before starting SNRI treatment.
- Monitor BP after initiation of treatment, after any subsequent dose increases, or initiation of other medicines associated with hypertension. If the patient has an approved home monitoring BP device this may be sufficient.
- Consider the following options if there is evidence of sustained hypertension (depending on the magnitude of the increase, patient response to treatment, general medical status): dose reduction or withdrawal, optimise or initiate antihypertensive treatment, reduction or withdrawal of any other current medications associated with hypertension.

Gabapentinoids: Pregabalin is licensed for treatment of peripheral or central neuropathic pain and gabapentin is licensed for the treatment of peripheral neuropathic pain only, but both are recommended by NICE for all neuropathic pain (except trigeminal neuralgia).

Suggested fast up-titration for Gabapentin:

Week 1		Week 2		Week 3
Day 1 to 2	300mg OD	Day 1 to 2	300 mg morning 300 mg midday 600 mg at night	600 mg TDS Continue this dose for further 2-3 weeks and review.
Day 3 to 4	300mg BD	Day 3 to 4	300 mg morning 600 mg midday 600 mg at night	
Day 5 to 7	300mg TDS	Day 5 to 7	600 mg TDS	

Consider slower increase in dose of gabapentin when patient presents symptoms of milder pain, they are elderly or have renal impairment. Also patients who are known to be sensitive to new medicines should follow slower titration process.

The plasma level of gabapentin does not increase proportionally with dose increase – this means that the risk of side effects is higher when high doses are taken. Moreover, bioavailability of gabapentin falls from 60% to 33% as the total daily dosage increase from 900mg to 3600 mg. For safety reasons the Nottinghamshire APC guideline recommends that the maximum daily dose of gabapentin should **NOT exceed 1800mg.**

Suggested up-titration for Pregabalin:

	Week 1	Week 2	Week 3
Morning	75 mg	150 mg	300 mg
Evening	75 mg	150 mg	300 mg

Caution in renal impairment: Both pregabalin and gabapentin go through minimal first-pass metabolism and are eliminated unchanged in the urine. Renal impairment will consequently decrease gabapentinoids

elimination and result in potential drug accumulation. It is a good practice to review (at least twice per annum) patients with declining kidney function known to be using gabapentinoids regularly. See local guidance on monitoring the renal function in patients over the age of 65 prescribed gabapentinoids. Manufacturer advises adjusting the dose of gabapentin and pregabalin in line with creatinine clearance level (ml/min).

Gabapentin in renal impairment (ref: Neurontin SPC):

Creatinine clearance (ml/min)	Dose regimen	Maximum total daily dose
≥80	300mg TDS - 600mg TDS	**900 - 1800mg**
50-79	200mg TDS - 600mg TDS	**600 - 1800mg**
30-49	100mg TDS - 300mg TDS	**300 – 900mg**
15-29	300mg every other day - 200mg TDS	**150 – 600mg**
<15*	300mg every other day - 100mg TDS	**150 – 300mg**

*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).

Pregabalin in renal impairment (ref: Lyrica SPC):

Creatinine clearance (ml/min)	Dose regimen	Maximum total daily dose
≥ 60	300mg BD - 200mg TDS	**600mg**
≥ 30 - < 60	150mg BD - 100mg TDS	**300mg**
≥ 15 - < 30	150mg OD - 75mg BD	**150mg**
< 15	75mg OD	**75mg**

Time for full response to treatment with gabapentinoids is usually 4-8 weeks. If found of little benefit to the patient, the dose should be tapered gradually. For gabapentin doses lower than 900mg a day reduce the total daily dose by 100mg every 4 days; for doses above 900mg reduce the total daily dose by 300mg every four days. Pregabalin should be tapered down by 50 to 75mg per week.

PAIN MEDICINES AND DRIVING

All clinicians should discuss a risk of pain medicines and impairment of driving skills. Useful information can be found on website of Faculty of Pain Medicine (see Driving and Pain) as well as on DVLA website.

Medicine	Typical daily starting dose	Maximum daily dose	Comments	Duration of adequate trial
TRICYCLIC ANTIDEPRESSANTS				
Amitriptyline	10 – 25 mg at night	75 mg at night	Take 90 – 120 minutes before going to bed. Response normally evident at 75 mg daily. Higher doses up to 150 mg only on recommendation from Pain Specialist. Do not stop abruptly – gradually titrate down.	6 – 8 weeks with at least 2 weeks at maximum tolerated dose
Nortriptyline	10 mg at night	75 mg at night	Take 90 – 120 minutes before going to bed. Increase gradually; higher doses to be given under specialist supervision. The dose should preferably be reduced gradually over about 4 weeks. OFF-LABEL USE.	6 – 8 weeks with at least 2 weeks at maximum tolerated dose
ANTIEPILEPTICS				
Carbamazepine	100 mg twice daily	200 mg four times a day	For initial treatment of **trigeminal neuralgia**. Increase slowly to 200mg 2-4 times daily. Avoid sudden withdrawal - gradually titrate down.	6 – 8 weeks with at least 2 weeks at maximum tolerated dose
Gabapentin	300 mg at night	600 mg three times a day	See page 7 for suggested titration regimen. NICE CKS rapid titration is less preferred locally. Side effects worst at times of dose increase. Do not stopabruptly – gradually titrate down.	3 – 8 weeks for titration plus two weeks at maximum dose
Pregabalin	75mg twice daily	300mg twice daily	Only if gabapentin ineffective or not tolerated. See page 7 - for suggested titration regimen. NICE CKS rapid titration is less preferred locally. Do not stop abruptly –gradually titrate down.	4-6 weeks
SNRI				
Duloxetine	30mg once daily for 2weeks then increase to 60mg once daily	120mg once daily or in two divided doses	Licensed for diabetic neuropathy only. Blood pressure monitoring recommended in patients with known hypertension and/or other cardiac disease, especially during first month Avoid in severe renal impairment (CrCl<30ml/min). Avoid abrupt withdrawal (withdraw slowly over min. of 1 to 2 weeks). Risk of serotonin syndrome if used concomitantlywith other serotonergic agents. May have small increase in fasting glucose / HbA1c. May increase LFTs. The plasma concentration of duloxetine displays large inter-individual variability. Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose (max 60mg BD).	8 weeks
OPIOIDS				
Tramadol	50 – 100 mg four times a day	100 mg four times a day	Consider tramadol for short periods only. Increased risk of seizure /serotonin syndrome when used in conjunction with TCA or SSRI. May cause less respiratory depressionand constipation than other opioids.	4 weeks
TOPICAL AGENTS				
Capsaicin	0.075%	3 – 4 timesdaily	For post herpetic neuralgia. Care on application (see patient information leaflet). Counseling required. Review at 8 weeks and only continue if benefit is seen.	8 weeks
Lidocaine 5% medicated plasters	One plaster(can be cut)	*Two plasters as recommended by the local Pain Team (although max licensed dose is 3 plasters)	**Amber 2** - on Pain Management Service recommendation only for localized neuropathic pain due to post herpetic neuralgia (PHN) only where oral treatments and capsaicin have been ineffective or are contraindicated. **Red-** for other conditions may only be prescribed in exceptional circumstances and by pain specialist prescribers. Up to two* plasters to be applied for 12 hours each day. Review after 4 weeks. If no significant decrease in pain or satisfactory increase in physical function, then it should be stopped.	4 weeks

RESOURCES FOR CLINICIANS AND PATIENTS

RESOURCE NAME	RESOURCE DESCRIPTION AND WEBSITE ADDRESS
NICE - Neuropathic pain in adults: pharmacological management in non-specialist settings (CG 173)	This guideline covers managing neuropathic pain (nerve pain) with pharmacological treatments (drugs) in adults in non-specialist settings. https://www.nice.org.uk/guidance/cg173
APC local guidelines for primary care within NHS Nottingham and Nottinghamshire CCG	https://www.nottsapc.nhs.uk/guidelinesformularies/
British National Formulary Online	https://bnf.nice.org.uk/
Live Well with Pain	An online resource for GPs and pain specialists to help increase skills and confidence in working with people who live with persistent pain. https://livewellwithpain.co.uk/
Opioids Aware	A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. https://www.fpm.ac.uk/opioids-aware
MHRA Drug safety updates	https://www.gov.uk/drug-safety-update
Moving Medicine	A useful resource to help healthcare professionals integrate physical activity conversations into routine clinical care. https://movingmedicine.ac.uk/
Faculty of Pain Medicine - PILs	Patient information leaflets on medications and interventions commonly used to treat persistent pain https://fpm.ac.uk/patients/patient-info
Pain Toolkit	https://www.paintoolkit.org/
Brief Pain Inventory	Screening Questionnaire http://www.npcrc.org/files/news/briefpain_short.pdf
Pain DETECT questionnaire	painDETECT-Questionaire-01.pdf (specialistpainphysio.com)
NHS How to get to sleep	Sleep restoration strategies https://www.nhs.uk/live-well/sleep-and-tiredness/10-tips-to-beat-insomnia/
Mind website	Explains sleep and mental health, gives practical suggestions and information about where to get support. https://www.mind.org.uk/information-support/types-of-mental-health-problems/sleep-problems/about-sleep-and-mental-health/
INSIGHT - Nottingham Mental Health Services Mid-Notts' (Mansfield and Ashfield, Newark, and Sherwood area)	Offers various support including CBT. This service is free, confidential and covers anyone 18+ years who are registered with a GP in the Nottinghamshire area. https://www.insightiapt.org/locations/nottingham/
Let's Talk – Wellbeing Nottingham City and parts of Nottinghamshire.	Let's Talk - Wellbeing is available to people aged 18 and over who are registered with a GP in Nottingham and parts of Nottinghamshire. https://www.nottinghamshirehealthcare.nhs.uk/ltwb-contact-us

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