PrescQIPP Community Interest Company

Neuropathic pain

Across England and Wales £111.7 million is spent annually on amitriptyline, duloxetine, gabapentin and pregabalin. (NHSBSA October 2020 to December 2020)

QIPP projects in this area are aimed at reviewing prescribing in neuropathic pain to ensure: a cost-effective pathway has been followed; cost-effective preparations have been used; when pregabalin is used, it is prescribed generically in capsule form for all indications; patients are regularly reviewed for treatment effectiveness and the need for deprescribing or changing treatment when appropriate.

Recommendations

- Agree a local neuropathic pain treatment pathway through an appropriate group, e.g. the area prescribing committee, involving all key stakeholders such as pain specialists, GPs, pharmacists, nurse prescribers and other healthcare professionals. See Attachment 1. Neuropathic pain - treatment pathway.
- Local neuropathic pain treatment pathway discussions should include consideration of: the preferred order of use of first line treatments (if more than one is suitable for the individual patient); treatment costs; whether combination therapies are supported and at what position in the treatment pathway; which treatments are supported for prescribing in primary care, specialist settings only and other locally agreed parameters.
- Neuropathic pain treatment plans should be agreed with patients taking into account their preferences, individual clinical circumstances, previous treatments tried, local treatment pathway choices, treatment reviews and when to stop treatment. See Attachment 4. Neuropathic pain - Patient Information Leaflet.
- Ensure patients understand where treatments are unlicensed and that informed consent is given. See Attachment 4. Neuropathic pain - Patient Information Leaflet.
- When initiating treatment, titrate doses gradually and increase to the maximum tolerated dose before considering switching or stopping treatment, if not effective.
- Consider the potential for misuse or illicit diversion before prescribing pregabalin, gabapentin or tramadol. Patients should be told about the risk of abuse and dependence. See Attachment 4. Neuropathic pain - Patient Information Leaflet.
- Ensure prescribed (and taken) doses of pregabalin and gabapentin are not outside the therapeutic dose range.
- Review treatment eight weeks after initiation and discontinue if ineffective (withdrawal from treatment should be gradual and cross-tapered with new treatment).
- Assess the need for continued treatment at each review, including the possibility of gradually reducing the dose if sustained improvement is observed.
- Ensure that all pregabalin and gabapentin prescriptions are written generically and as capsules (rather than tablets) for all indications.
- When pregabalin is used, prescribe a twice daily dosing schedule rather than three times daily as this is more convenient for patients and for most daily doses is more cost-effective.

Recommendations

- Do not offer pregabalin and gabapentin for managing sciatica as there is no overall evidence of benefit and there is evidence of harm.
- Where nortriptyline tablet doses of 50mg or 75mg are needed, use multiples of 25mg tablets as the nortriptyline 50mg tablets are more costly.

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic wellbeing. Neuropathic pain is defined as 'pain caused by a lesion or disease of the somatosensory nervous system'. Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'.[1]

Neuropathic pain is often difficult to treat because it is resistant to many medications and/or because of the adverse effects associated with effective medications.[2] Neuropathic pain symptoms are subjective with wide variation in reported prevalence.[1] No single medicine works for all neuropathic pain, and given the diversity of pain mechanisms, patients' responses and diseases, treatment must be individualised.[2]

Non-pharmacological treatments include, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist services). Self management options need to be examined and reviewed at every opportunity.[1]

Other than analgesia, factors to consider when individualising therapy include tolerability; other benefits (e.g. improved sleep, mood, and quality of life); co-morbidities; concomitant therapies and contraindications; low likelihood of serious adverse events and cost effectiveness to the patient and the health economy.[1,2]

National guidance and clinical effectiveness

The NICE Clinical Guideline, Neuropathic pain in adults: pharmacological management in non-specialist settings [CG173] recommends to:

"Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)".[1]

The full guideline explains that the Guideline Development Group (GDG) was unable to consider a single pharmacological treatment as clearly superior to all alternatives. They agreed to make their recommendations on the basis that the sequential strategy with the highest probability of cost effectiveness for any individual patient is to try treatments in order of their individual probability of cost effectiveness.[1]

Looking at the cost effectiveness of the treatments, the GDG found that gabapentin had the highest net benefit, which is why it was recommended as an initial treatment option. Amitriptyline had closely comparable costs per QALY to gabapentin and lower net costs so was also recommended as an initial treatment option.[1]

Pregabalin and duloxetine were recommended as initial treatment options due to their wider licences. However at the time of writing the GDG did acknowledge that both these treatments represented poor value for money and further stated:

"Probabilistic sensitivity analysis showed a negligible probability that either of these options provides greatest net benefit at conventional QALY values. For these reasons, the GDG felt it would not be possible to support recommendations that suggested either option as an initial treatment for neuropathic pain. However, the GDG noted that, when compared with placebo alone (that is, no treatment), both drugs appeared to be viable options from a health economic point of view. Therefore, it would be appropriate to recommend these treatments in a context where other options were removed

from the decision-space that is, when they are contraindicated or when they have been tried and proven ineffective or were not tolerated".[1]

The costs of generic pregabalin, gabapentin and duloxetine have significantly reduced since this analysis by the GDG was undertaken. Generic versions of pregabalin, gabapentin and duloxetine are now available in the Drug Tariff, as category M or A preparations.[3]

The All Wales Medicines Strategy Group (AWMSG) has produced the resource, "Persistent Pain Resources, Ten Key Messages", which was last updated in December 2020. This resource lists ten key messages on the treatment of neuropathic pain. The suggested drug treatments are those set out in the NICE clinical guidance on neuropathic pain in adults: pharmacological management in non-specialist settings [CG173].[4]

The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of chronic pain (SIGN 136) published in December 2013 and last revised in August 2019, recommends amitriptyline and gabapentin as first line drug choices in neuropathic pain. Pregabalin is an alternative in patients not benefitting from, or not tolerating, amitriptyline or gabapentin. An alternative tricyclic antidepressant such as imipramine or nortriptyline is recommended if amitriptyline does not produce effective results. A selective noradrenaline reuptake inhibitor (SNRI), such as duloxetine, is an alternative to trying a different tricyclic antidepressant. Carbamazepine is recommended for use as a first-line agent in trigeminal neuralgia. Low-dose topical capsaicin is not included in the pathway because SIGN found no good evidence for its' use. Opioids are recommended only in carefully selected and screened patients. Use of long acting preparations, avoiding breakthrough dosing and no higher dose than 180mg morphine or equivalent is recommended. Treatment should be discontinued if not effective.[5]

In Northern Ireland, the Health and Social Care Board make recommendations on the treatment of non-malignant neuropathic pain in non-specialist settings for new patients in their treatment algorithm. They recommend amitriptyline tablets first line followed by gabapentin capsules if amitriptyline is unsuitable, not tolerated or unsuccessful. Amitriptyline should be stopped slowly. If treatment with gabapentin is unsuitable, not tolerated or unsuccessful (and amitriptyline has already been considered or tried) consider duloxetine or pregabalin (stop gabapentin slowly). If either is unsuitable, unsuccessful or not tolerated, stop slowly and consider the remaining drug.[6]

A Cochrane review of amitriptyline for neuropathic pain in adults found 17 studies which included 1,342 participants covering seven neuropathic conditions. The studies were of very low quality evidence. There is limited evidence based on small numbers of small studies that amitriptyline may have some benefit in neuropathic pain, with the exception of cancer-related and HIV-related neuropathic pain. Combining the classic neuropathic pain conditions of painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), and mixed neuropathic pain for third-tier evidence* gave, in four studies and 382 participants, a statistically significant benefit for amitriptyline compared with placebo (RR 2.0 (1.5 to 2.8)), with an NNT of 5.1 (3.5 to 9.3). This is probably an overestimation of treatment effect, but the magnitude and consistency of effect within these studies does provide some confidence that amitriptyline benefits are real, at least for some people. More participants experienced at least one adverse effect; 55% of patients taking amitriptyline compared to 36% taking placebo. Serious adverse events were rare. The authors concluded that amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many people with neuropathic pain. There is no good evidence of a lack of effect; rather the concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain, but only a minority of people will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all.

*The third tier of evidence used data from fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation

concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.[7]

A Cochrane review of duloxetine for treating painful neuropathy, chronic pain or fibromyalgia published in 2014 found eight studies which included 2,728 participants with painful diabetic neuropathy. Duloxetine at 60mg daily was found to be effective in treating painful diabetic peripheral neuropathy in the short term, with a risk ratio (RR) for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08). The related number needed to treat for an additional beneficial outcome (NNTB) was 5 (95% CI 4 to 7). There was no effect on central neuropathic pain in a single, small, high quality trial. In all conditions, adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect. Most adverse effects were minor, but 12.6% of participants stopped the drug due to adverse effects. Serious adverse events were rare.[8]

An Australian RADAR review concluded that pregabalin appears to have similar efficacy to that of amitriptyline and gabapentin for neuropathic pain from indirect comparisons; there are no head-to-head trials comparing the efficacy of pregabalin with that of other drugs for neuropathic pain. Consider initial treatment with another analgesic adjuvant, such as a tricyclic antidepressant before pregabalin.[9]

An updated Cochrane review looked at gabapentin in chronic neuropathic pain in adults. This was an update to a 2014 review which included an additional four new studies with 530 participants and excluded three previously included studies (126 participants). In total, the 2017 review considered 37 studies (5,914 participants).[10]

In post herpetic neuralgia, more participants (32%) had substantial benefit (at least 50% pain relief or Patient Global Impression of Change scale (PGIC) very much improved) with gabapentin at 1200mg daily or greater than with placebo (17%). RR 1.8 (95% CI 1.5 to 2.1); number needed to treat (NNT) 6.7 (5.4 to 8.7); from eight studies, 2,260 participants, with moderate-quality evidence. More participants (46%) had moderate benefit (at least 30% pain relief or PGIC much or very much improved) with gabapentin at 1200mg daily or greater than with placebo (25%) (RR 1.8 (95% CI 1.6 to 2.0); NNT 4.8 (4.1 to 6.0).

In painful diabetic neuropathy, more participants (38%) had substantial benefit (at least 50% pain relief or PGIC very much improved) with gabapentin at 1200mg daily or greater than with placebo (23%). RR 1.7 (95% CI 1.4 to 2.0); NNT 6.6 (5.0 to 10); from six studies, 1,331 participants, with moderate-quality evidence. More participants (52%) had moderate benefit (at least 30% pain relief or PGIC much or very much improved) with gabapentin at 1200mg daily or greater than with placebo (37%). RR 1.4 (95% CI 1.3 to 1.6); NNT 6.6 (4.9 to 9.9); from seven studies, 1,439 participants, with moderate-quality evidence.

For all conditions combined, adverse event withdrawals were more common with gabapentin (11%) than with placebo (8.2%). RR 1.4 (95% CI 1.1 to 1.7); (number needed to harm) NNH 30 (20 to 65); from 22 studies, 4,346 participants, with high-quality evidence. Serious adverse events were no more common with gabapentin (3.2%) than with placebo (2.8%). RR 1.2 (95% CI 0.8 to 1.7); from 19 studies, 3,948 participants, with moderate-quality evidence. There were eight deaths (very low-quality evidence). Participants experiencing at least one adverse event were more common with gabapentin (63%) than with placebo (49%). RR 1.3 (95% CI 1.2 to 1.4); NNH 7.5 (6.1 to 9.6); from 18 studies, 4,279 participants, with moderate-quality evidence. Individual adverse events occurred significantly more often with gabapentin. Participants taking gabapentin experienced dizziness (19%), somnolence (14%), peripheral oedema (7%), and gait disturbance (14%).[10]

A 2019 Cochrane review assessed the analgesic efficacy and adverse effects of pregabalin for chronic neuropathic pain in adults.[11] The review included 45 studies (11,906 participants) lasting two to 16 weeks.

In postherpetic neuralgia, more participants had at least 30% pain intensity reduction with pregabalin 300mg than with placebo (50% vs. 25%; RR 2.1 (95% confidence interval (CI) 1.6 to 2.6); NNTB 3.9 (3.0 to 5.6); from three studies (589 participants), with moderate-quality evidence). More had at least 50% pain intensity reduction (32% vs 13%; RR 2.5 (95% CI 1.9 to 3.4); NNTB 5.3 (3.9 to 8.1); from four studies (713 participants), with moderate-quality evidence).

More participants had at least 30% pain intensity reduction with pregabalin 600mg than with placebo (62% vs. 24%; RR 2.5 (95% CI 2.0 to 3.2); NNTB 2.7 (2.2 to 3.7); from three studies (537 participants), with moderate-quality evidence). More had at least 50% pain intensity reduction (41% vs. 15%; RR 2.7 (95% CI 2.0 to 3.5); NNTB 3.9 (3.1 to 5.5); from four studies (732 participants), with moderate-quality evidence). Somnolence and dizziness were more common with pregabalin than with placebo (moderate-quality evidence): somnolence with 300mg 16% vs. 5.5%, 600 mg 25% vs. 5.8%; dizziness with 300mg 29% vs. 8.1%, 600mg 35% vs. 8.8%.

In painful diabetic neuropathy more participants had at least 30% pain intensity reduction with pregabalin 300mg than with placebo (47% vs. 42%; RR 1.1 (95% CI 1.01 to 1.2); NNTB 22 (12 to 200); from 8 studies (2,320 participants), with moderate-quality evidence). More had at least 50% pain intensity reduction (31% vs. 24%; RR 1.3 (95% CI 1.2 to 1.5); NNTB 22 (12 to 200); from 11 studies (2,931 participants), with moderate-quality evidence). More had PGIC much or very much improved (51% vs. 30%; RR 1.8 (95% CI 1.5 to 2.0); NNTB 4.9 (3.8 to 6.9); from five studies, 1,050 participants, with moderate-quality evidence).

More participants had at least 30% pain intensity reduction with pregabalin 600mg than with placebo (63% vs. 52%; RR 1.2 (95% CI 1.04 to 1.4); NNTB 9.6 (5.5 to 41); from two studies (611 participants), with low-quality evidence). More had at least 50% pain intensity reduction (41% vs. 28%; RR 1.4 (95% CI 1.2 to 1.7); NNTB 7.8 (5.4 to 14); from five studies (1,015 participants), with low-quality evidence). Somnolence and dizziness were more common with pregabalin than with placebo (moderate-quality evidence): somnolence with 300mg 11% vs. 3.1%, 600mg 15% vs. 4.5%; dizziness with 300mg 13% vs. 3.8%, 600mg 22% vs. 4.4%.

In mixed or unclassified post-traumatic neuropathic pain more participants had at least 30% pain intensity reduction with pregabalin 600mg than with placebo (48% vs. 36%; RR 1.2 (1.1 to 1.4); NNTB 8.2 (5.7 to 15); from four studies (1,367 participants), with low-quality evidence). More had at least 50% pain intensity reduction (34% vs. 20%; RR 1.5 (1.2 to 1.9); NNTB 7.2 (5.4 to 11); from four studies (1,367 participants), with moderate-quality evidence). Somnolence (12% vs. 3.9%) and dizziness (23% vs. 6.2%) were more common with pregabalin.

In central neuropathic pain more participants had at least 30% pain intensity reduction with pregabalin 600mg than with placebo (44% vs. 28%; RR 1.6 (1.3 to 2.0); NNTB 5.9 (4.1 to 11); from three studies (1562 participants), with low-quality evidence). More patients also had at least 50% pain intensity reduction (26% vs. 15%; RR 1.7 (1.2 to 2.3); NNTB 9.8 (6.0 to 28); from three studies, 562 participants, with low-quality evidence). Somnolence (32% vs. 11%) and dizziness (23% vs. 8.6%) were more common with pregabalin.

In other neuropathic pain conditions studies show no evidence of benefit for 600mg pregabalin in HIV neuropathy (two studies (674 participants), moderate-quality evidence) and limited evidence of benefit in neuropathic back pain or sciatica, neuropathic cancer pain or polyneuropathy.

Serious adverse events were no more common with placebo than with pregabalin 300mg (3.1% vs. 2.6%; RR 1.2 (95% CI 0.8 to 1.7); from 17 studies, 4,112 participants, with high-quality evidence) or pregabalin 600mg (3.4% vs. 3.4%; RR 1.1 (95% CI 0.8 to 1.5); 16 studies (3,995 participants), with high-quality evidence).[11]

A systematic review and meta-analysis conducted by the International Association for the Study of Pain (IASP) concluded that tricyclic antidepressants, duloxetine, gabapentin or pregabalin could all be recommended as first-line treatments in neuropathic pain. NNTs (for 50% pain relief) were 7.7 for pregabalin, 6.3 for gabapentin, 6.4 for duloxetine. The NNT was lower for tricyclic antidepressants at 3.6, this was based mainly on use of amitriptyline.[12]

As part of a surveillance review of NICE clinical guideline on neuropathic pain [CG173], in September 2020, NICE reviewed the evidence on treating sciatica and added new recommendations on pharmacological treatment to the NICE guideline on low back pain and sciatica [NG59] as well as

research recommendations on sciatica. The guidance recommends to not offer gabapentinoids (pregabalin and gabapentin), other antiepileptics, oral corticosteroids or benzodiazepines for managing sciatica as there is no overall evidence of benefit and there is evidence of harm. It also recommends to not offer opioids for managing chronic sciatica. As part of shared decision making about whether to stop opioids, gabapentinoids or benzodiazepines for sciatica, the clinician should discuss the problems associated with withdrawal with the person.[13]

Treatment review

The NICE clinical guideline [CG173] recommends early and regular assessment for patients prescribed treatments for neuropathic pain. The early review after starting or changing treatment needs to include dosage titration, tolerability and adverse effects to assess suitability of chosen treatment.[1]

In addition, regular clinical reviews should be conducted to assess and monitor effectiveness of chosen treatment and need to include assessment of:

- Pain control
- Adverse effects
- Impact on lifestyle, daily activities (including sleep disturbance) and participation (such as ability to work and drive)
- Physical and psychological wellbeing
- Continued need for treatment.[1]

Organisations may use questionnaires such as PainDETECT or the Leeds Assessment of Neuropathic Signs and Symptoms (LANNSS) to identify if neuropathic pain is likely (see links in appendix 1 - pain screening tools and questionnaires).

In the majority of cases, a medicine should be reduced gradually and stopped if the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose.[14]

Assess the need for continued treatment at each review, including the possibility of gradually reducing the dose if sustained improvement is observed.[1]

For pregabalin and gabapentin, if treatment is successful, it is suggested that there should be a reduction on an annual basis to ascertain ongoing effectiveness.[15]

Licensed indications

- Amitriptyline is licensed for the treatment of neuropathic pain in adults.[16]
- Duloxetine is licensed for diabetic neuropathy in adults.[16]
- Gabapentin is licensed for peripheral neuropathic pain in adults.[16]
- Pregabalin is licensed for peripheral and central neuropathic pain in adults.[16]
- Capsaicin 0.075% cream (Axsain®) is licensed for post-herpetic and painful diabetic neuropathy (under expert supervision) in adults.[16]
- Tramadol is licensed for moderate to severe pain in adults and children from 12 years old.[16]
- Lidocaine 5% plasters are licensed for postherpetic neuralgia in adults.[16]
- Nortriptyline is not licensed for use in neuropathic pain, but a neuropathic pain indication and dose is listed in the British National Formulary (BNF).[16]

Several treatments are used outside of their product licences, sometimes referred to as ‘off label use’. If a decision is made to prescribe the medicines for unlicensed indications, prescribers should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained, documented and patients should be given information about the unlicensed/off label status of their prescribed medicines.[1]

Pregabalin patent issues

NHS England issued guidance on prescribing and dispensing pregabalin in 2015 following a patent dispute between Warner-Lambert Company LLC and a number of generic pharmaceutical suppliers. That guidance has now been withdrawn and replaced with updated guidance, which came into force on 17 July 2017. This states 'When dispensing pregabalin for the treatment of any condition, you should dispense in accordance with your normal practice'.[17]

Pregabalin capsules and tablets are now included in the Drug Tariff as Category M for the capsules and Category A for the tablets which indicates that generic versions are readily available. Pregabalin 20mg/ml oral solution sugar free is Category C where the price is based on the brand (Lyrica®).[3]

Gabapentin and pregabalin risk of misuse

Gabapentin and pregabalin are structurally similar drugs acting via the alpha-2-delta subunit of voltage-gated calcium channels. There is published evidence that both gabapentin and pregabalin are subject to abuse and misuse.[15,18]

Both medicines have known psychiatric side effects.[19,20] Individuals misusing gabapentin and pregabalin variably describe improved sociability, euphoria, relaxation and a sense of calm. Gabapentin and pregabalin can cause depression of the central nervous system (CNS), resulting in drowsiness, headache, sedation, respiratory depression and at the extreme, death. These adverse effects are additive when used with other centrally acting drugs, particularly opioids.[15] Where patients are receiving concomitant opioids they should be monitored for signs of CNS and/or respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.[19]

In addition:

- The Summary of Product Characteristics (SPC) for pregabalin states that cases of abuse, dependence and misuse have been reported. Caution should be exercised when prescribing in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.[20]
- The SPC for gabapentin states that cases of abuse and dependence have been reported in the gabapentin post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.[19]

The pharmacokinetic properties of pregabalin make it relatively more dangerous than gabapentin in high doses.[15] Pregabalin misusers take large quantities, ranging from 200mg to 5g as a single dose (note - the recommended therapeutic dose range is 150mg to 600mg daily).[15,20]

Pregabalin and gabapentin are included in the list of medicines at high risk of misuse, diversion and dependence in prison. It is recommended that they are taken under supervision, arrangements made to check compliance and generally not prescribed to drug users unless prescribing is absolutely necessary, as they are typically sold and abused. For the treatment of neuropathic pain in prisons, the Royal College of General Practitioners (RCGP) recommend avoiding initiation of pregabalin and gabapentin and review and reduce current prescriptions where possible. Where prescribed, use of twice daily dosing is recommended to facilitate supervised consumption.[21]

The current 'Pain management formulary for prisons' recommends that amitriptyline is used as a first line agent for neuropathic pain in prisons.[22] Duloxetine is recommended as a second line formulary choice. Nortriptyline, gabapentin, pregabalin and tramadol have been designated as limited use when other options have failed.[22]

Pregabalin and gabapentin as Schedule 3 controlled drugs

In April 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) published a Drug Safety Update notifying healthcare professionals that pregabalin and gabapentin are now controlled

under the Misuse of Drugs Act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3. It is illegal for people to possess pregabalin and gabapentin without a prescription and illegal for a patient to supply or sell them to others.[23]

Schedule 3 drugs are subject to special prescription requirements; in addition to normal prescription requirements for prescription only medicines (POMs), prescriptions for schedule 3 drugs must also contain:[24]

- Dose (which must be clearly defined; 'as directed' is not acceptable)
- Date on which it was signed
- Address of the prescriber
- Formulation
- Strength (where appropriate)
- Total quantity or dosage units of the preparation in both words and figures
- An appropriate date: prescriptions are valid for 28 days after the appropriate date on the prescription. The appropriate date is either the signature date or any other date indicated on the prescription (by the prescriber) as a date before which the drug should not be supplied – whichever is the later.

It is strongly recommended that the maximum quantity of Schedule 3 drugs prescribed should not exceed 30 days. Prescribers should not issue repeatable prescriptions for Schedule 3 drugs.[24] The MHRA advises healthcare professionals to evaluate patients carefully for a history of drug abuse before prescribing pregabalin and gabapentin and observe patients for development of signs and abuse and dependence.[23]

Other treatment options

Combination therapy

The NICE full guideline on the management of neuropathic pain in adults [CG173] acknowledged that combination therapy is commonly used in practice and may be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs.[1] However, combination therapy is not listed as a treatment option. Instead combination therapy is recommended for further research as there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations.[1] The NICE Clinical Knowledge Summary on neuropathic pain goes further and recommends against the use of combination drugs in neuropathic pain, 'Do not prescribe more than one neuropathic pain drug at the same time. For example, do not prescribe amitriptyline concurrently with duloxetine, gabapentin, or pregabalin'.[14]

In contrast, the SIGN clinical guideline on the management of chronic pain recommends that combination therapies should be considered for patients with neuropathic pain.[5] Annex 3, a neuropathic pain pathway, states that if initial agents do not help it is appropriate to change to an alternative agent, either as a sole agent or in combination with one or more drugs known to be effective in neuropathic pain, such as a gabapentinoid (or opioid in appropriate cases). Generally two types of antidepressant are not given together unless one is in low dose (e.g. amitriptyline 25mg) or on specialist advice.[5]

There is a risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed together. Prescribers should be aware of the increased risk of side effects and also drug interactions when two drugs are prescribed together.[16]

Patients on combination therapies should be reviewed for effectiveness and tolerability. In line with reviewing monotherapy for benefit at eight weeks, it would seem reasonable to review combination therapy at the same interval. As with monotherapy, medicines should be gradually reduced and stopped if the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated doses.[14]

Tramadol

The NICE clinical guideline on neuropathic pain [CG173] recommends to consider tramadol only if acute rescue therapy is needed. Tramadol long-term is not recommended in non-specialist settings and must not be used.[1] The Clinical Knowledge Summary on neuropathic pain states that for people awaiting referral after initial treatments have failed, consider prescribing a short course of tramadol for pain relief. Prescribe tramadol cautiously, bearing in mind the potential for misuse.[14] Tramadol is a Schedule 3 controlled drug.[16] For further information on prescribing opioids in pain, such as the risks of dependence and addiction, refer to the PrescQIPP pain webkit.

Capsaicin cream

Capsaicin 0.075% cream is recommended for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments in the NICE CG173.[1] The GDG considered there was some evidence that capsaicin 0.075% cream is better than placebo at reducing pain compared to other topical treatments. However, the GDG noted that it takes some time to learn how to apply the cream correctly (they noted that using gloves and/or avoiding particularly sensitive areas such as the eyes is often advised).[1]

In contrast, the SIGN guideline 136 states that few studies of low dose cream were identified, but it appears to have no benefit over placebo cream for patients with neuropathic pain.[5]

As capsaicin 0.075% cream (Axsain®) has a UK marketing authorisation for post-herpetic neuralgia and painful diabetic peripheral polyneuropathy, use for other conditions would be off-label.[1] The SPC states that this should only be used for painful diabetic peripheral polyneuropathy 'under the direct supervision of a hospital consultant who has access to specialist resources'.[25] The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.[1]

Nortriptyline

The NICE clinical guideline on neuropathic pain [CG173] states that nortriptyline consistently reduced pain compared with placebo, but there was much uncertainty around these estimates.[1] NICE states that whilst the mean cost-per-QALY appeared to represent poor value for money, the GDG did not exclude the possibility that it may be an extremely effective option and noted that in seven of 10 safety network meta-analyses it appeared to be somewhat better tolerated than amitriptyline with lower incidence of adverse events.[1] However, nortriptyline is not included in the main recommendations. At the time of the guideline development, nortriptyline was significantly more costly than amitriptyline. Now, however, the costs have reduced for nortriptyline 10mg and 25mg tablets (but not the 50mg tablets).[3]

A Cochrane review found six studies for nortriptyline treating 310 participants with various neuropathic pain conditions. The studies were small and had one or more sources of potential major bias. Very low quality evidence indicated similar efficacy to other active interventions (gabapentin, morphine, chlorimipramine, amitriptyline) and to placebo. More participants reported adverse events with nortriptyline than with placebo, similar numbers with nortriptyline and amitriptyline, chlorimipramine and gabapentin and slightly more than morphine. No serious adverse events or deaths were seen. The authors concluded that there is little evidence to support the use of nortriptyline to treat neuropathic pain conditions and effective medicines with much greater supportive evidence are available such as duloxetine and pregabalin.[26]

The BNF suggests that nortriptyline may be better tolerated than amitriptyline in neuropathic pain, an unlicensed indication.[16]

Lidocaine plasters

NICE CG 173 does not make a recommendation about the use of lidocaine plasters for neuropathic pain. This is because the GDG felt that there was not enough evidence on lidocaine that met the review

protocol inclusion criteria to warrant a specific recommendation. A research recommendation on the efficacy and tolerability of topical lidocaine in neuropathic pain was made.[1]

Further information, including a review of the evidence and spend on lidocaine plasters is available in the PrescQIPP bulletin 200: Lidocaine plasters.[27]

In 2017, NHS England recommended that lidocaine plasters should not routinely be prescribed in primary care. Lidocaine plasters are classified as an item of low clinical effectiveness where there is a lack of robust evidence of clinical effectiveness or there are significant safety concerns.[28]

The British Pain Society suggest that if a person is referred to a specialist pain service and their expert advice is to use lidocaine 5% plasters then treatment should continue to be funded in primary care. People prescribed lidocaine 5% plasters should have their treatment reviewed to assess efficacy.[29]

In 2008 the Scottish Medicines Consortium (SMC) accepted lidocaine medicated plasters for restricted use within NHS Scotland. It is accepted for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia). Use is restricted to those intolerant of first-line systemic therapies for post-herpetic neuralgia or where these therapies have been ineffective. The SMC noted that comparative data for lidocaine plasters are limited, and comparative clinical effectiveness was unclear.[30]

The SIGN guideline on chronic pain recommends that lidocaine plasters are the topical agent of choice in the non-specialist setting in patients with neuropathic pain who prefer a topical treatment. Up to three plasters can be used at a time. If there is no improvement after four weeks, then they should be discontinued.[5]

Commencing and switching between first line treatments

When offering a choice of amitriptyline, duloxetine, gabapentin and pregabalin, the CKS on neuropathic pain advises to titrate the dosage according to response and tolerability.[14] A local neuropathic pain treatment pathway may be produced with suggested dosage titration regimens. Attachment 1 may be used or adapted locally for this purpose.

The NICE guidance on neuropathic pain [CG173] recommends when withdrawing or switching treatment, to taper the withdrawal regimen to take account of dosage and any discontinuation symptoms. Detailed advice on how to taper doses is not provided.[1] The following advice is available on treatment tapering and withdrawal:

- The CKS on neuropathic pain suggests that if treatment is not effective or not tolerated:[14]
  - » Use clinical judgement to decide whether to titrate the dose more slowly upwards instead of switching (especially if adverse effects improve with time following each dose increase).
  - » When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.
- The tricyclic antidepressants (TCAs), amitriptyline and nortriptyline, should be withdrawn gradually over about four weeks or longer if withdrawal symptoms emerge. Withdrawal effects may occur within five days of stopping treatment with antidepressants. Symptoms are usually mild and self-limiting, but in some cases may be severe.[16]
- The dose of duloxetine should be reduced over at least one to two weeks. The most common withdrawal symptoms from duloxetine are nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances and tremor.[16]
- Gabapentin should be discontinued gradually over a minimum of one week in accordance with current clinical practice.[19]
- Pregabalin should be withdrawn over at least one week and abrupt withdrawal avoided.[16]

- The CKS on depression provides advice on switching from a tricyclic antidepressant (TCA) to a different TCA or to another type of antidepressant. A direct switch from amitriptyline to nortriptyline is possible.[31]
- Switching from amitriptyline/nortriptyline to duloxetine requires cautious cross-tapering starting with low dose duloxetine.[31]

Recommendations for switching between first line treatment options may be considered locally and included in local treatment pathways. Attachment 1, the neuropathic pain treatment pathway may be used for this purpose.

Specialist referral

Consider referring the person to a specialist pain service and/or a relevant clinical specialty (for example neurology, diabetology, or oncology) if they have:

- Severe pain.
- Their pain significantly limits their 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.[14]

Implementation resources

A treatment pathway incorporates information from the NICE clinical guideline on neuropathic pain [CG173], the SPCs and specific treatments for trigeminal neuralgia and diabetic neuropathy. The pathway is in attachment 1 and can be used and adapted locally. This may be used as a template for discussion by the local Area Prescribing Committee involving all key stakeholders such as pain specialists, GPs, pharmacists, nurse prescribers and other healthcare professionals. A locally adaptable 'Invitation to Review' letter is in attachment 2. An audit is available in attachment 3 to assist with reviewing neuropathic pain prescribing.

Further resources are also available in the PrescQIPP pain webkit.

Costs and savings

Across England and Wales £111.7 million is spent on amitriptyline, duloxetine, gabapentin and pregabalin. (NHSBSA October 2020 to December 2020)

QIPP savings arise from:

- Prescribing cost-effective preparations
- Reviewing patients at eight weeks and discontinuing treatment if ineffective
- Gradually reducing the dose if sustained improvement is observed.

If 5% of patients with neuropathic pain were reviewed and a dose reduction attempted or treatment discontinued if ineffective/not tolerated, then this could **save approximately £5.6 million annually across England and Wales.**

Table 1 illustrates the comparative costs for treatments used for neuropathic pain, including the NICE CG173 first line treatment choices, amitriptyline, duloxetine, gabapentin and pregabalin.[1]

Comparative costs for pregabalin using twice daily dosing and three times daily dose are given in table 1. Most twice daily pregabalin regimens are less costly or have similar costs to three times daily dosing regimens and may be more convenient for patients.

The cost of generic nortriptyline 50mg tablets are significantly more costly than the 10mg or 25mg tablets.[3] To meet daily dosage requirements, prescribe 10mg or 25mg tablets (and multiples thereof) where possible and not 50mg tablets.

Across England and Wales £1.36 million was spent on nortriptyline 50mg tablets. (NHSBSA October 2020 to December 2020). Prescribing two 25mg tablets instead of one 50mg nortriptyline tablet could **save £1.25 million across England and Wales or £1,954 per 100,000 population** (NHSBSA October 2020 to December 2020).

Table 1. 28 day cost comparisons for neuropathic pain treatments

Drug preparation	Dose range[16]	Cost per 28 days[3,16]
Amitriptyline tablets	10mg – 75mg at night	£1.08 - £2.83 (Using 1 x 25mg tablet plus 1 x 50mg tablet for 75mg dose)
Duloxetine gastro-resistant capsules	60mg – 120mg daily	£2.36 - £4.72
Pregabalin capsules	150mg – 600mg daily (2 or 3 divided doses)	£2.23 - £4.32 (Twice daily dosing) £2.99 - £4.98 (Three times daily dosing)
Lyrica® (pregabalin) capsules	150mg – 600mg daily (2 or 3 divided doses)	£64.40 (Twice daily dosing) £96.60 (Three times daily dosing)
Gabapentin capsules	300mg – 1.2g three times daily	£2.90 - £15.41
Nortriptyline tablets (unlicensed use)	10mg – 75mg at night	£1.03 - £3.52 (Using 3 x 25mg tablets for 75mg dose) £1.03 - £40.35 (Using 1 x 25mg tablet plus 1 x 50mg tablets for 75mg dose)
Capsaicin 0.075% cream	Apply three to four times a day	£27.22 - £36.29 (Assume 1g used per application)
Tramadol immediate release capsules	50mg - 100mg every 4 to 6 hours up to a maximum of 400mg/24 hours -acute short term use	£3.73 - £7.46 (Using 50mg capsules and a 200mg - 400mg daily dose)

Table 2 illustrates the cost difference between generic and branded pregabalin capsule preparations. Prescribing pregabalin capsules generically is the least costly pregabalin option.

The costs for the most expensive pregabalin brand, Lyrica®, are included in table 2 to illustrate the extra expense when this brand is prescribed compared to generic pregabalin.

Across England and Wales £3.6 million is spent on the Lyrica® brand annually. (NHSBSA October 2020 to December 2020) Switching from Lyrica® to generic pregabalin could **save £3.3 million annually across England and Wales or £5,188 per 100,000 population.**

Table 2: Comparative costs of generic and branded pregabalin capsules[3,16]

Product	Cost for 28 days (One capsule twice daily)				
	Lyrica®	Alzain®	Lecaent®	Axalid®	Generic pregabalin capsules
Pregabalin 25mg capsules	£64.40	£4.99	Discontinued	£19.95	£2.06
Pregabalin 50mg capsules	£64.40	£5.99	Discontinued	£19.95	£1.87
Pregabalin 75mg capsules	£64.40	£5.99	Discontinued	£19.95	£2.17
Pregabalin 100mg capsules	£64.40	£4.66	£64.39	£19.95	£2.40
Pregabalin 150mg capsules	£64.40	£6.99	Discontinued	£19.95	£3.01
Pregabalin 200mg capsules	£64.40	£8.99	Discontinued	£19.95	£3.12
Pregabalin 225mg capsules	£64.40	£7.99	Discontinued	£19.95	£3.54
Pregabalin 300mg capsules	£64.40	£8.99	Discontinued	£19.95	£4.73

Table 3 illustrates that pregabalin tablets are more costly than pregabalin capsules for all strengths. Pregabalin should be prescribed generically in the capsule form in preference to pregabalin tablets where this is suitable for the individual patient. Currently, £207,172 is spent annually on all strengths of pregabalin tablets across England and Wales. Switching from pregabalin tablets to pregabalin capsules could **save £157,452 across England and Wales or £247 per 100,000 population.** (NHSBSA October 2020 to December 2020) Patients on pregabalin tablets should be identified for suitability for a switch to generic pregabalin capsules.

Table 3: Comparative costs of generic pregabalin capsules and tablets

Pregabalin strength	Formulation	Cost for 56 doses[3]	Cost pressure of using tablets rather than capsules
Pregabalin 25mg	Capsules	£1.92	108% increase
	Tablets	£3.99	
Pregabalin 50mg	Capsules	£1.99	34% increase
	Tablets	£2.66	
Pregabalin 75mg	Capsules	£2.23	115% increase
	Tablets	£4.79	
Pregabalin 100mg	Capsules	£2.39	56% increase
	Tablets	£3.73	
Pregabalin 150mg	Capsules	£2.79	100% increase
	Tablets	£5.59	
Pregabalin 200mg	Capsules	£3.32	44% increase
	Tablets	£4.79	
Pregabalin 225mg	Capsules	£3.41	87% increase
	Tablets	£6.39	
Pregabalin 300mg	Capsules	£4.32	66% increase
	Tablets	£7.19	

An audit (attachment 3) can be used to identify patients who would be suitable for a neuropathic pain therapy review.

An audit tool used for the prescribing of these medicines in prisons is also available on the Specialist Pharmacy Services website.[32]

A patient information leaflet is available which may be issued when treatment is initiated or reviewed (attachment 4). This may be adapted for local use.

Summary

- A neuropathic pain treatment pathway should include an agreed preferred order of use of first line treatments (if more than one is suitable for the individual patient); cost-effective treatment choices; whether combination therapies are supported and if so, at what position in the treatment pathway; which treatments are supported for prescribing in primary care, specialist settings only and other locally agreed parameters.
- Prescribing for neuropathic pain treatments should be reviewed following the criteria in the NICE clinical guideline management of neuropathic pain in adults [CG173] and discontinued (gradually) if ineffective.
- Pregabalin and gabapentin are now Schedule 3 controlled drugs. They have the potential to be abused by individuals with a history of substance abuse (particularly when prescribed with opioids, or in those recently released from secure environments) and prescribing should be reviewed considering this. Any prescribing should also be within recommended therapeutic dose ranges.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-216-neuropathic-pain/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B216_Neuropathicpain/FrontPage?:iid=1&:isGuestRedirectFromVizportal=y&:embed=y

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The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer). Terms and conditions

Appendix 1. Pain screening tools and questionnaires

- PainDETECT
  http://www.specialistpainphysio.com/wp-content/uploads/2010/07/painDETECT-Questionaire-01.pdf
- Leeds Assessment of Neuropathic Signs and Symptoms (LANSS)
  http://www.endoexperience.com/documents/Apx4_LANSS.pdf