Neuropathic pain: a pathway for care developed by the British Pain Society

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Summary. Neuropathic pain is a common chronic pain condition that can be challenging to treat, particularly for non-specialists. The development of the Map of Medicine care pathway for the management of neuropathic pain was led by the British Pain Society. Focusing on treatment by non-specialists, this pathway is based on new evidence, consensus, and the interests of service users. This paper presents the care pathway and accompanying evidence base, highlighting its salient features, and discussing important treatment points. After initial assessment, the pathway progresses through first-, second-, and third-line drug treatment, includes advice on topical treatment and opioids (in specific circumstances), and describes non-pharmacological approaches. Importantly, timely review of patients and referral to specialist secondary or tertiary care must be considered as vital components of the pathway. Although the emphasis was not on specialist treatment, advice is given on existing interventions, including neural stimulation and multi-disciplinary care. These, and other steps on the pathway, will be subject to further review as more evidence becomes available. In the meantime, the pathway represents a straightforward, valuable and accessible approach for healthcare professionals managing the distress and impact of neuropathic pain.

Keywords: nerve pain; neuralgia; neuropathic pain

The British Pain Society (BPS) is a national society, affiliated with the International Association for the Study of Pain (IASP). It has commissioned working groups to develop five care pathways for pain to assist the management of common pain conditions. The pathways are intended to be comprehensive and to maximize generalist care, and each has an accompanying commentary. They are: the initial assessment and early management of pain; chronic widespread pain, including fibromyalgia; low back, and radicular pain; pelvic pain; and neuropathic pain (presented here). They can be viewed on the BPS website. The pathways were chosen because of the high frequency of presentation with the problem, geographical variability in access to treatment, variation in clinical case management, or a combination of some or all of these issues.

Neuropathic pain

Neuropathic pain is a particularly unpleasant type of pain, whose characteristics contribute to poor general health, and produce quality of life scores similar to those reported by people with serious mental illness, or with severe heart disease. In common with other chronic conditions, it is commoner among women and in relative deprivation. The ageing population and rising prevalence of specific risk factors (notably diabetes) mean that neuropathic pain will increase both in incidence and prevalence, and it is important

Neuropathic pain, defined by the IASP as ‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory system’, was previously thought to affect 1% of the UK population, but more recent research suggests that this figure is closer to 8%. This increase is due in part to the recognition that neuropathic mechanisms contribute to many types of chronic pain, and therefore that ‘classic’ neuropathic pain diagnoses (Table 1) only represent a small proportion of the problem in the population. It is also likely that patients and professionals are more aware of the possibility of neuropathic pain than they were, perhaps because of greater availability of specific, effective treatments, and educational initiatives surrounding these.

Neuropathic pain is a common chronic pain condition that can be challenging to treat, particularly for non-specialists. The development of the Map of Medicine care pathway for the management of neuropathic pain was led by the British Pain Society. Focusing on treatment by non-specialists, this pathway is based on new evidence, consensus, and the interests of service users. This paper presents the care pathway and accompanying evidence base, highlighting its salient features, and discussing important treatment points. After initial assessment, the pathway progresses through first-, second-, and third-line drug treatment, includes advice on topical treatment and opioids (in specific circumstances), and describes non-pharmacological approaches. Importantly, timely review of patients and referral to specialist secondary or tertiary care must be considered as vital components of the pathway. Although the emphasis was not on specialist treatment, advice is given on existing interventions, including neural stimulation and multi-disciplinary care. These, and other steps on the pathway, will be subject to further review as more evidence becomes available. In the meantime, the pathway represents a straightforward, valuable and accessible approach for healthcare professionals managing the distress and impact of neuropathic pain.

Editor’s key points

- Neuropathic pain is a challenging pain syndrome to treat effectively.
- Diagnosis of neuropathic pain can be ‘possible’, ‘probable’, or ‘definite’, all potentially requiring treatment.
- This review outlines a new practical guideline to the comprehensive management of neuropathic pain.
- The current evidence base has clear research gaps that need to be addressed.
Therefore that non-specialist health professionals have a robust, evidence-based approach to its management.

Excellent recent systematic reviews have assessed the evidence for pharmacological treatment of neuropathic pain, concluding that there are many specific effective medicines available.\textsuperscript{15, 16} Other systematic approaches have produced evidence-based consensus approaches to the assessment of neuropathic pain, in both primary care,\textsuperscript{17} and other settings.\textsuperscript{18} Despite this, there is consistent evidence of under-recognition, under-treatment of neuropathic pain, or both, particularly in primary care.\textsuperscript{15, 20} Hall and colleagues, in a 2005 review of common neuropathic pain conditions using the General Practice Research Database, found that the most commonly prescribed items were the same across conditions, and included opioids as first-line treatments. However, changes in therapy were less frequent when initial therapy was with antidepressants or anticonvulsants rather than conventional analgesics, confirming the relative effectiveness of these drugs in primary care.\textsuperscript{21} Therefore, there is a need for accessible guidance for non-specialists, to help them to improve the health and quality of life of their patients with the best approaches to treating this common and disabling condition.

With all guidelines, the most important step in achieving the intended outcome is the first one having identified its relevance (i.e. setting off on the correct pathway). This is the stage at which undifferentiated illness (as usually presented in primary care) takes on shape and form, achieves definition, and moves towards diagnosis and management. This is particularly true for neuropathic pain, recognition of which (as distinct from non-neuropathic pain) leads to the use of effective treatments and the avoidance of some ineffective ones. Along the way, this is likely to lead to the maximum clinical benefit, with the minimal harm. Arguably, therefore, the most important activities associated with good quality guidelines are those that promote awareness of their existence, enhance their accessibility, or both.

The recent re-classification of neuropathic pain by the IASP, now makes this first step easier. Previously, a binary clinical entity (present/absent), the diagnosis of which relied on detailed neurological assessment, we now acknowledge the existence of ‘possible’, ‘probable’, and ‘definite’ neuropathic pain.\textsuperscript{9} Although still requiring skilled clinical history and examination, the diagnosis of ‘possible’ neuropathic pain requires less time and specialist clinical skill, and is therefore easier in brief primary care consultations. The presence of a few typical symptoms and easily observed signs, with a neuro-anatomically logical potential cause, is sufficient for the non-specialist to take the first steps towards successful management, using available guidelines.\textsuperscript{17} In this way, gauging response to early, specific treatments, reduces suffering, and assists diagnosis, often without the need for the detailed assessment that might be required to diagnose ‘definite’ neuropathic pain.

### Table 1: Common causes of neuropathic pain

<table>
<thead>
<tr>
<th>Peripheral</th>
<th>Central</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful diabetic neuralgia</td>
<td>Post-stroke pain</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Multiple sclerosis</td>
<td>Neuropathic contributions to other painful conditions</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Chemotherapy-induced pain</td>
<td></td>
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<tr>
<td>Lumbar radiculopathy</td>
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<tr>
<td>Nerve damage, including postoperative</td>
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<tr>
<td>Pain because of cancer tumour infiltration</td>
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### Aims and objectives of the neuropathic pain pathway

The neuropathic pain pathway was developed in response to the need highlighted above, and with the intention of maximum accessibility and reading ease. It aims to take the non-specialist from the point of recognizing ‘possible’ neuropathic pain through an evidence-based series of management options to the point at which the pain (a) is managed satisfactorily, (b) resolves, or (c) requires specialist secondary care assessment and intervention. There is also guidance on treatments and management to be used within specialist settings, which though less specific than the guidance for non-specialist management, will inform General practitioners (GPs) and others involved in shared care, and guide specialist practice. Important features include: (i) the use of a limited set of first- and second-line drugs; (ii) the parallel use of non-pharmacological approaches, self-help, and highlighted information resources; (iii) need for early and frequent review at the outset of treatment to ensure that maximum effective/tolerated treatment is given as quickly as possible; (iv) need for early specialist secondary care referral in severe or uncertain disease without awaiting the end of the pathway (but also for the pathway to continue while the specialist assessment is awaited); and (v) information on secondary care interventions, drugs used with specialist supervision, and multidisciplinary pain management.

The pathway has been developed in collaboration between the Map of Medicine editorial team, representatives of the BPS and independent reviewers. It is based on well-reputed secondary evidence, as selected in accordance with the Map of Medicine’s editorial methodology for developing care pathways. Practice-based knowledge has been added by clinicians nominated by the BPS and by independent reviewers identified by the Map of Medicine editorial team. For the detailed editorial methodology please see the Neuropathic Pain Pathway provenance certificate (see Appendix 1, Supplementary material). Map of Medicine care pathways can be customized to reflect local commissioning needs and practices to provide comprehensive, evidence-based local guidance and clinical decision.
support at the point of care. This article is complementary to the published pathway.

Discussion and practice points

The neuropathic pain care pathway is shown in Figure 1. Several discussion and practice points are discussed below.

Comparison with National Institute of Health and Clinical Excellence guidance (for details see: www.nice.org.uk.CG96)

The pathway is similar in many ways, up to the point of specialist secondary care referral, to recent guidance produced in the UK by National Institute of Health and Clinical Excellence (NICE) for the pharmacological management in non-specialist settings (currently under review). NICE guidelines set evidence-based standards for healthcare, focus on costs and benefits, and are adopted as the standard for practice in the NHS in England. However, this pathway is broader than the NICE guidance, aiming to provide an overview of all relevant management approaches, in a format that can be used in other healthcare settings, while still retaining the basis in current evidence. With respect to recommended pharmacological treatment, important differences from NICE include this pathway’s recommendation of gabapentin, a range of tricyclic antidepressants or carbamazepine among drugs in first-line treatment (NICE recommends pregabalin or amitriptyline, or duloxetine specifically in painful diabetic neuropathy). Topical treatment (e.g. capsaicin 0.075% cream) for localized areas of neuropathic pain is included in this pathway, but not in the NICE guidance. These treatments are simple and logical, even though evidence for their effectiveness is less robust than for oral medications. NICE specifies that strong opioids should only be prescribed in collaboration with specialist care; this pathway includes strong opioids in third-line treatment, but highlights the importance of competence and experience in their use, and suggests adherence to the BPS’s guidelines. The pathway also considers non-pharmacological approaches, and includes recommendations for patient information resources and team approaches including links to other pathways. It is important that much of the evidence for non-pharmacological treatment is not specific to neuropathic pain. We need to be speculative in extrapolating evidence from non-specific studies to neuropathic pain, but consensus and clinical experience provide good reason to believe that the recommendations in this pathway will be helpful nonetheless, pending the necessary research. Some are based on evidence assimilated in other NICE guidelines. Finally, this pathway includes some treatments that may be more relevant outside some primary care settings. There is now good evidence for the effectiveness of the capsaicin 8% patch (in post-herpetic neuralgia), but this still requires specialist supervision. Other drugs such as lidocaine, or those requiring local injection, are probably for the specialist arena only, as, are surgical techniques or implants. It is helpful for non-specialists to know about the existence and the use of these approaches, both to inform the timing of referral, and their discussions with patients beforehand and afterwards.

How do we define a non-specialist?

Both the NICE guidance and this pathway are intended for use by ‘non-specialists’. In this context, ‘specialist’ refers to a professional’s knowledge, experience and resources for managing neuropathic pain. So, while most ‘non-specialist’ doctors will be general practitioners, the pathway is also aimed at consultants and others expert in their own special field (e.g. diabetes and orthopaedics), who need to know how to manage a patient with neuropathic pain, according to current standards. Professionals who manage neuropathic pain all the time, already working according to international standards, can deviate from the pathway according to their specialist knowledge. They are also likely to be those furnishing the details of the final parts of the pathway, including supervising specific medications, coordinating multi-disciplinary interventions and providing surgical treatments.

Initial assessment

Some helpful practical advice about the clinical presentation and the diagnosis of neuropathic pain is provided. As highlighted above, this will alert the physician to the presence of possible neuropathic pain. A brief but careful history and examination is the key to this diagnosis, along with an awareness of the need to consider neuropathic mechanisms in anyone presenting with pain. Simple screening tools, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANS) and PainDETECT, are available to assist in diagnosis, but are not considered a substitute for these basic clinical skills, and their positive predictive value in the primary care setting is unknown. These questionnaire instruments share elements in common with the advice provided in the pathway. Questions about altered sensation and numbness in the area of pain, evoked, or spontaneous pain sensations of unpleasant character (e.g. ‘shooting’ or ‘burning’ pains) are important. Similarly, the demonstration of absent or altered sensation in the relevant area, in response to pinprick, vibration, hot, or cold pressure, or simple touch is important. The extent to which a practitioner will be able to test these will depend on the context in which he/she is working, but minimal testing should always be possible, allowing the decision on whether to embark on the pathway.

Reviewing progress

An important point that recurs in the pathway (and NICE guidance) is recommendations for the interval between reviewing changes in medication. These are important in determining when to move from first- to second- then third-line treatment. A maximum review period of 2 weeks after initiating any treatment is specified. This allows: (i) the assessment of any effectiveness of the new treatment in improving symptoms; (ii) the titration of dose as required; and (iii) the assessment of any adverse reactions and the response to these. In most cases, the starting dose will be lower than the maximum tolerated
Possible neuropathic pain – clinical presentation

History and examination

Red flag and 4D risk assessment

If criteria are met, refer urgently to specialist

Develop and agree a management plan with the patient including ongoing assessment

Go to complex regional pain syndrome

First-line treatment

Topical treatment for focal neuropathies

Second-line treatment

Add in tramadol as third-line treatment

Review if not improved, and consider referral for further specialized diagnostic testing

Refer for specialized diagnostic testing

Confirm diagnosis and consider multi-disciplinary team (MDT) referral

Develop and agree a management plan with patient including ongoing assessment

Consider interventional pain therapies and medications that require specialized supervision

Provide a multi-disciplinary review to consider treatment options

Fig 1 The neuropathic pain care pathway
effective dose, and this early review will optimize the interval to achieve this, thereby minimizing suffering. Another important timing point is that at which specialist referral (if required) is made. In summary, this should be immediate if the pain is severe, causing significant distress, if any ‘red flag’ factors are present, or if diagnosis is difficult. Crucially, treatment should continue, according to the pathway, while specialist review is awaited. Otherwise, specialist referral should be made after third-line treatment is proved unsatisfactory, if diagnostic uncertainty remains, or both, with a maximum of 6 months as the initiation of first-line treatment. Again, treatment should continue, for example, with the introduction of strong opioids in accordance with BPS guidelines and according to the physician’s experience and skills. These approaches are intended to reduce the occurrence of refractory neuropathic pain, which is associated with particular suffering, disability, and healthcare use.11

**Complex regional pain syndrome**

Complex regional pain syndrome (CRPS) is a chronic condition that is notoriously difficult to treat successfully. Formerly known as reflex sympathetic dystrophy or causalgia, it manifests as pain, swelling, and skin changes, and is associated with a complex cluster of physical, emotional, and social problems. Our understanding of CRPS has been growing at a rapid rate with a greater knowledge of the neural pathways involved and the treatments that are likely to be successful, which were summarized in a recently published set of guidelines.30 Previously, CRPS was thought of as a specific type of neuropathic pain, but it is now generally considered to be a distinct clinical entity. However, there are overlaps with neuropathic pain in some of the pathophysiological and presenting features and in the agreed approach to its management. The care pathway group, therefore, chose to ‘signpost’ this important topic as it may respond well to early management consistent with the pathway.

**Topical treatments**

The pathway recommends use of topical treatments for localized causes of neuropathic pain, such as post-herpetic neuralgia, perhaps even before first-line treatment is given. This is at odds with the NICE guidance, which concluded that: (i) there was insufficient evidence to support the general use of weak topical agents, such as capsaicin 0.075% cream or lidocaine patches; and (ii) capsaicin 8% patches (for which the evidence is stronger) are currently intended for specialist use.28 They are included in this with the principle that ‘no absence of effectiveness is not equivalent to evidence of ineffectiveness’. Systemic agents cause significant side-effects and drop-out from treatment is therefore common. There is good clinical consensus that topical agents are effective in certain circumstances, they may prevent the need for systemic therapies and contingent adverse reactions and interactions, and there was strong patient-representative preference expressed for their use during the development of the pathway. Finnerup and colleagues51 recommended the use of topical therapies for focal, peripheral neuropathic pain, based upon the relative balance between Number Needed to Treat and Number Needed to Harm. They are not useful for widespread neuropathic pain, and systemic therapy should be added or substituted quickly in the event of non-response.

**Gabapentin as first choice**

This pathway recommends gabapentin among the choice of first-line drugs. There was controversy with the publication of the NICE guidance on the recommendation of pregabalin in preference to gabapentin in first-line treatment of neuropathic pain. Gabapentin is probably cheaper to supply and possibly of equivalent efficacy. However, the conclusion reached by NICE, based on their review of economic evidence, was that pregabalin was more cost effective, because of simpler administration and titration regimes, and the lower incidence of adverse effects, leading to fewer healthcare attendances.22 However, as noted above, these findings are now being reviewed.

There is growing concern about the development of gabapentin and pregabalin as drugs of abuse, with exponential increase noted in rates of its prescription and relatively high rates of use by attenders at substance misuse services.32 There are no controls on the prescribing of gabapentin, over and above those for other prescription only medicines, and physicians need to be aware of this potential for harm in addition to those listed in the standard drug information.

**Carbamazepine**

The pathway makes a clear recommendation for using carbamazepine as first-line therapy in the case of trigeminal neuralgia. The studies of carbamazepine’s efficacy date back to the 1960s and are well summarized in the American Academy of Neurology’s guidelines on the management of this condition.33 There are some subsequent comparison studies described in this guideline and subsequently,34 but the studies have small numbers of recruits. The NICE neuropathic pain guidelines made several suggestions for further research in this area to confirm the clinical suspicion that carbamazepine holds its place as first-line therapy. Until this has been done, there is little argument to make any change from current recommendations.

**Strong opioids**

The use of strong opioids in chronic non-malignant pain, including neuropathic pain, is controversial, but their judicious use is recommended in later parts of this pathway. Before prescribing strong opioids, the prescriber should screen for risk of an addiction disorder, either based upon the history or using a standard screening tool. Additionally, evidence is emerging from US studies of the importance of maintaining a ceiling morphine equivalent dose of no more than 120 mg in adults and 50 mg in the elderly, and prescribing modified release preparations only.35 36

There is reasonable evidence for the effectiveness of strong opioids in the short- and medium-term, and though long-term effectiveness remains incompletely assessed, there is good...
is their potential for harm, including sedation, constipation, hyperalgesia, reduced immunity, hormone suppression, and dependence. Therefore, their use should be restricted to refractory cases and to supervision by physicians experienced in their use and the assessment of the associated risks and outcomes. Excellent guidance on this is available, as a consensus between the BPS and the Royal Colleges of Anaesthetists, General Practitioners, and Psychiatrists. Key to this is detailed discussion with patients at the outset of treatment, including agreed treatment goals, and knowledge of equivalent doses between different opioids.

Adopting a multi-disciplinary approach
The pathway has emphasized the importance of the interdisciplinary and multi-specialty approach in secondary care and beyond; also, that there should be an agreed management plan with the patient and shared care as appropriate. NICE guidelines for neuromodulation and pain (Spinal Cord Stimulation and Deep Brain Stimulation) are available and are noted in the specialist part of the pathway.

The pathway has not attempted to cover in depth the treatments that should be considered in specialist secondary care and beyond because this working group considered the focus of the BPS care pathways to be non-specialist care. The evidence to support these approaches is growing and, in future versions of the pathway, it may become appropriate to separate these treatments out from the others provided in specialist care. The use of neurostimulation should be considered with caution as the evidence for efficacy was based upon relatively short-term studies, with some longer-term cohort studies suggesting a diminution of effect. Complex combinations of analgesics need careful supervision because of the potential for adverse effects and interactions. There is a relative paucity of evaluation of standard psychological interventions specifically for neuropathic pain, and therefore they are recommended largely to address the impact of pain. Neuropathic radicular pain is considered in the low back pain pathway published in this issue of the JBA.

Conclusions
This pathway provides a useful approach to the management of neuropathic pain by non-specialists, and indicates approaches that may be used in specialist secondary care. With a basis in existing sources of best evidence and consensus, it gives the opportunity for confidence in addressing this challenging and unpleasant clinical condition, while also paying attention to the co-morbidities that often accompany it. The keys to its successful implementation, at the individual level, are attention to the patient’s specific needs, early review of the response to any treatment and referral for specialist assessment when it is clear that treatment is not working. In this way, combining professional healthcare skills with the pathway outlined here, the burden of neuropathic pain on our patients can be reduced.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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References
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