GUIDELINES

Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Why read this summary?

Neuropathic pain is often difficult to treat as it is resistant to many medications and effective medications often have adverse effects. Its estimated prevalence is between 1% and 2% in the United Kingdom.[1] Treatment practice is thought to vary considerably throughout the UK in terms of starting treatment, achievement of therapeutic doses, and correct sequencing of therapeutic classes, thus probably leading in some cases to inadequate pain control, with considerable morbidity. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on drug management for neuropathic pain in adults in primary and secondary care, excluding specialist pain services.[2]

Recommendations

NICE recommendations are based on systematic reviews of best available clinical and cost effectiveness evidence. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice including, in this guidance, lessons derived from other clinically relevant fields. Evidence levels for the recommendations are given in italic in square brackets.

The following definitions apply to this guideline:

Specialist pain services—Services that provide comprehensive assessment and multimodal management of all types of pain, including neuropathic pain

Non-specialist settings—Primary and secondary care services (including general practice, general community care, and hospital care) that do not provide specialist pain services

Condition specific services—Services that provide treatment for the underlying health condition that is causing neuropathic pain (examples include neurology, diabetology, and oncology services).

Key principles of care

- Consider referring the person to a specialist pain service and/or a condition specific service at any stage (including initial presentation and regular clinical reviews) if:
  - The pain is severe or
  - The pain substantially limits daily activities and participation, for example, in interpersonal interactions and in domestic, community, social, and civil life[3] or
  - Any underlying health condition has deteriorated.
- Continue existing treatments for people whose neuropathic pain is already effectively managed.
- Respond to the person's concerns and expectations when agreeing which treatments to use by discussing:
  - The benefits and possible adverse effects of each drug treatment
  - Why a particular drug treatment is being offered
  - Coping strategies for pain and for possible adverse effects of treatment
  - Availability of non-drug treatments—for example, surgical treatments and psychological therapies—in non-specialist settings and/or through referral to specialist services.
- Explain both the importance of dosage titration and the titration process, providing written information if possible.
- When selecting drug treatments, take into account:
  - The person's vulnerability to specific adverse effects because of comorbidities or age—for example, vulnerability to falls
  - Safety considerations and contraindications as detailed in the "summary of product characteristics"
  - The patient's preference
  - Lifestyle factors, such as occupation
  - Any mental health problems, such as depression and/or anxiety
  - Any other medication the person is taking.
- When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.
- When introducing a new treatment, consider an overlap with the existing treatment(s) to avoid deterioration in pain control.
- After starting or changing a treatment, do an early clinical review of dosage titration, tolerability,

and adverse effects to assess the suitability of the chosen treatment.
- Do regular clinical reviews to assess and monitor the effectiveness of the chosen treatment. Each review should assess:
  - Pain reduction
  - Adverse effects
  - Daily activities and participation, such as ability to work and drive
  - Mood (in particular, whether the person may have depression and/or anxiety; refer to relevant NICE guidelines as necessary)[4-6]
  - Quality of sleep
  - Overall self reported improvement.

[*All the above recommendations are based on the experience and opinion of the Guideline Development Group*]

First line treatment

- Offer oral amitriptyline or pregabalin as first line treatment (except for people with painful diabetic neuropathy):
  - Amitriptyline: start at 10 mg a day, gradually titrating upwards to an effective dose or to the person's maximum tolerated dose, with no dose higher than 75 mg a day (higher doses could be considered in consultation with a specialist pain service)
  - Pregabalin: start at 150 mg a day (divided into two doses; a lower starting dose may be appropriate for some people), titrating upwards to an effective dose or to the person's maximum tolerated dose, with no dose higher than a total 600 mg a day.
- For people with painful diabetic neuropathy offer oral duloxetine as first line treatment; if duloxetine is contraindicated—for example, owing to uncontrolled hypertension or to renal impairment—offer oral amitriptyline:
  - Duloxetine: start at 60 mg a day (a lower starting dose may be appropriate for some people), titrating upwards to an effective dose or to the person's maximum tolerated dose, with no dose higher than 120 mg a day
  - Amitriptyline: as in the recommendation above.

[*All the above recommendations are based on high or moderate quality randomised controlled trials and cost effectiveness evaluation*]
- On the basis of both the early and regular clinical reviews, do the following:
  - If improvement is satisfactory, continue the treatment; consider gradually reducing the dose over time if improvement is sustained
  - If amitriptyline as first line treatment reduces the pain satisfactorily but the person cannot tolerate the adverse effects, consider oral imipramine or nortriptyline as an alternative.

[*Based on the experience and opinion of the Guideline Development Group*]

Second line treatment

- If pain reduction is not satisfactory with first line treatment at the maximum tolerated dose, offer treatment with another drug type instead of or in combination with the original drug, after informed discussion with the person:
  - If the first line treatment was amitriptyline (or imipramine or nortriptyline), switch to or combine with oral pregabalin
  - If the first line treatment was pregabalin, switch to or combine with oral amitriptyline (or imipramine or nortriptyline as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects).
- For people with painful diabetic neuropathy:
  - If the first line treatment was duloxetine, switch to amitriptyline or pregabalin or combine with pregabalin
  - If the first line treatment was amitriptyline, switch to or combine with pregabalin.
- Dosage and titration should be the same as given in the recommendations for first line treatment.

[*All the above recommendations are based on high or moderate quality randomised controlled trials and cost effectiveness evaluation*]

Third line treatment

- If pain reduction is not satisfactory with second line treatment, refer the person to a specialist pain service and/or a condition specific service, and while waiting for referral:
  - Consider oral tramadol as a third line treatment instead of or in combination with the second line treatment; tramadol combined with amitriptyline, nortriptyline, imipramine or duloxetine is associated with only a low risk of serotonin syndrome (features of which include confusion, delirium, shivering, sweating, changes in blood pressure, and myoclonus)
  - Consider topical lidocaine for localised pain in people unable to take oral medication because of medical conditions and/or disability; topical lidocaine is licensed for post-herpetic neuralgia but not for other neuropathic pain.
- For tramadol as monotherapy, start at 50-100 mg not more often than every four hours, titrating upwards if required to an effective dose or to the person's maximum tolerated dose, with no dose higher than 400 mg a day. If tramadol is used as combination therapy, more conservative titration may be required.

[*Both the above recommendations are based on moderate or low quality randomised controlled trials and on the experience and opinion of the Guideline Development Group*]

Other treatments

- Do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition specific service.

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- Reducing the risk of venous thromboembolism in patients admitted to hospital (2010;340:c95)
- Depression in adults, including those with a chronic physical health problem (2009;339:b4108)
- When to suspect child maltreatment (2009;339:b2689)
- Early management of persistent non-specific low back pain (2009;338:b1805)
- Recognition and assessment of coeliac disease in children and adults (2009;338:b1684)

FURTHER INFORMATION ON THE GUIDANCE

Many people require treatment with more than one drug, but the correct choice of drugs, and the optimal sequence for their use, has been unclear. The guideline aims to provide clear recommendations to healthcare professionals in non-specialist settings on the management of neuropathic pain. This includes recommendations on appropriate and timely referral to specialist pain services and/or condition specific services. In general, regarding neuropathic pain as a "blanket condition," irrespective of the underlying cause, is helpful and practical for both non-specialist healthcare professionals and patients. This guideline should be used in conjunction with clinical judgment and decision making appropriate for the individual patient.

Methods

This guideline was developed as a short clinical guideline. Short clinical guidelines give recommendations on part of a care pathway and are intended to allow the rapid (over 9-11 months) development of guidelines for areas of care for which the NHS requires urgent guidance. Short clinical guidelines are developed by the NICE technical team using the same methods as the existing standard NICE guidelines developed by the National Collaborating Centres (www.nice.org.uk).

As part of this process, the NICE technical team conducted a systematic search of the literature, assessed the quality of included studies, synthesised and presented the evidence using the modified GRADE system. The Guideline Development Group (comprising healthcare professionals and patient representatives) then discussed the evidence and drew up recommendations. NICE has produced three different versions of the short clinical guideline: a full version, a quick reference guide, and a version for patients and the public. All versions are available on the NICE website.[2]

Further research

- What is the clinical and cost effectiveness of carbamazepine as first line treatment for trigeminal neuralgia compared with other, better tolerated drug treatments?
- What is the clinical effectiveness, cost effectiveness, and tolerability of monotherapy compared with combination therapy for treating neuropathic pain?
- What are the key factors, including additional care and support, that influence participation and quality of life in people with neuropathic pain?
- How should the symptomatic treatment of neuropathic pain relate to its cause?

- Drug treatments other than those recommended in this guideline that are started by a specialist pain service or a condition specific service may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements, and careful management of adverse effects.

[*Both the above recommendations are based on moderate or low quality randomised controlled trials and the experience and opinion of the Guideline Development Group*]

Overcoming barriers

Currently, healthcare professionals in non-specialist settings may use various guidelines and algorithms that are not consistent with this NICE guidance in managing neuropathic pain. Hence, implementing this NICE guidance may change current practices, particularly in drug treatment for painful diabetic neuropathy. Nevertheless, these recommendations are justifiable on the basis that most guidelines produced by other organisations, in contrast to NICE, were not compiled using a systematic and transparent evidence assessment system such as GRADE (grading of recommendations assessment, development, and evaluation) and did not consider cost effectiveness to reflect whether drugs used for neuropathic pain are a good use of NHS resources.

The Guideline Development Group comprised Peter Barry (chair), Tracey Cole, Paula Crawford, Peter Crome, Niru Goenka, Clair Haslem (resigned from the group after meeting 3), John Lee, Vera Neumann, David Rowbotham, Blair H Smith, and Heather Wallace. The NICE Short Clinical Guideline Technical Team comprised Mark Baker, Emma Banks, Nicole Elliott, Michael Heath, Vicky Kelly, Stefanie Reken, Beth Shaw, and Toni Tan.

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1 Bowsher D, Rigge M, Sopp L. Prevalence of chronic pain in the British population: a telephone survey of 1037 households. *Pain Clin* 1991;4:223-30.
2 National Institute for Health and Clinical Excellence. *Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings*. 2010 (Clinical guideline 96.) www.nice.org.uk/CG96.
3 World Health Organization. Towards a common language for functioning, disability and health: ICF—the international classification of functioning, disability and health. 2002. www.who.int/classifications/icf/training/icfbeginnersguide.pdf.
4 National Institute for Health and Clinical Excellence. *Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care [with amendment]*. 2004 (amended 2007). (Clinical guideline 22). www.nice.org.uk/CG22.
5 National Institute for Health and Clinical Excellence. *Depression: the treatment and management of depression in adults (update)*. 2009. (Clinical guideline 90.) www.nice.org.uk/CG90.
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10-MINUTE CONSULTATION

Sexual health consultation for men who have sex with men

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- Treatment for lymph node tuberculosis (2010;340:c63)
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- Reduced level of consciousness from baclofen in people with low kidney function (2009;339:b4559)
- Osteoarticular infection of the symphysis pubis and sacroiliac joints in active young sportsmen (2009;339:b5019)

A 28 year old man goes to his general practitioner for a general check up including tests for sexually transmitted infections. He discloses that he has had sex with men and is worried that a recent contact may have HIV. He has never been tested and has no genitourinary symptoms.

The unease a patient may associate with attendance at a genitourinary clinic means this presentation in general practice may be the only opportunity to manage him. General practitioners need to be conscious of their attitudes to men who have sex with men and of how comfortable they are taking their sexual history. It would be helpful to have information about local sexual health services as well as the post-exposure prophylaxis policy and provision by your accident and emergency department at hand.

What you should cover

Ask what prompted him to come for testing. Some specific significant event may be responsible, for example contact with someone with HIV (see box).

Ask about regular and casual partner(s) and associated sexual activities. Explain why you need to know before asking because, unless the question is placed in context, the patient may not disclose relevant information.

Oral sex is very often unprotected so it won't affect the discussion of sexually transmitted infections and throat swabs. Take anal swabs from those who have had receptive anal sex or received rimming (oral-anal sex).

Ask about the use of condoms and the context of sex (for example under the influence of drugs or alcohol or in the presence of depression). A man may choose not to use condoms when he is in a complex power hierarchy (for example where there is a large age difference) or if he is unrealistically optimistic (thinking he would not be so unlucky as to contract disease).

Ask about knowledge of post-exposure prophylaxis for HIV and history of sexually transmitted infections.

Ask about: dysuria or urethral discharge; anal pain, bleeding, or discharge; and genital ulcers. Ask specifically about rash because syphilis is increasingly common and the rash may be mild and self limiting.

What you should do

- Examine for ulcers (herpes or syphilis) or warts. In the absence of symptoms, physical examination will usually be normal.
- Test first pass urine for chlamydia and take a throat swab for gonorrhoea. For those who practise anal sex, anal swabs should be gently introduced (3-5 cm) and tested for chlamydia and gonorrhoea.
- Take blood for syphilis serology.
- Offer all patients an HIV test. Explain the window period and find out how well supported the patient is in case of a positive result. Discuss the benefits of testing and how the result will be given.

Risky behaviours for HIV infection

High risk
Unprotected anal sex with partner known to be HIV positive
Unprotected anal sex
Comorbid high risk behaviour (such as needle sharing)

Medium risk
Mixing alcohol, sex, and drugs

Low risk
Unprotected oral or oral-anal sex

- Start post-exposure prophylaxis for HIV as early as possible (no later than 72 hours after the risky event) if indicated.
- If symptoms of urethritis are present, consider empirical treatment before the results become available.
- If immunisation status is not documented, offer a blood test to check for hepatitis A and B. Consider human papillomavirus vaccination depending on the chance of previous infection.
- Offer risk reduction counselling appropriate to the social context (acknowledge for example that it may be difficult for a married man who has sex with men to carry condoms), and invite the patient to reflect on his motivation and (if relevant) reluctance to change behaviour. Provide information about support services.
- Encourage the patient to re-attend at least annually for screening for sexually transmitted infections and HIV even if he remains asymptomatic.
- If the patient is at significant ongoing risk of HIV exposure, consider referring him to the local sexually transmitted infections clinic for intensive risk reduction counselling.
- Have an action plan prepared in case of positive results, including counselling support, further testing, and contacting your local sexual health clinic for advice.

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USEFUL RESOURCES

British Association for Sexual Health and HIV (www.bashh.org/guidelines)
Centers for Disease Control and Prevention (www.cdc.gov/std/treatment/2006/toc.htm)
International Union Against Sexually Transmitted Infections (www.iusti.org/regions/Europe/euroguidelines.htm)
National Guideline Clearinghouse (www.guideline.gov)
Melbourne Sexual Health Centre (www.mshc.org.au/syphilis)
Terrence Higgins Trust (www.tht.org.uk/informationresources)

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs