NICE National Institute for Health and Care Excellence

NICE guideline

Neuropathic pain in adults: pharmacological management in non-specialist settings

Clinical guideline

Published: 20 November 2013
www.nice.org.uk/guidance/cg173

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guideline replaces CG96.

Overview

This guideline covers managing neuropathic pain (nerve pain) with pharmacological treatments (drugs) in adults in non-specialist settings. It aims to improve quality of life for people with conditions such as neuralgia, shingles and diabetic neuropathy by reducing pain and promoting increased participation in all aspects of daily living. The guideline sets out how drug treatments for neuropathic pain differ from traditional pain management.

MHRA advice on pregabalin and gabapentin: In July 2019 we updated footnotes in this guideline to reflect a change in the law relating to pregabalin and gabapentin. As of 1 April 2019, because of a risk of abuse and dependence pregabalin and gabapentin are controlled under the Misuse of Drugs Act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3.

MHRA advice on valproate: In April 2018, we added warnings that valproate must not be used in pregnancy, and only used in girls and women when there is no alternative and a pregnancy prevention plan is in place. This is because of the risk of malformations and developmental abnormalities in the baby. See update information for details.

Who is it for?

- Healthcare professionals
- Adults with neuropathic pain, their families and carers

Introduction

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. The International Association for the Study of Pain (IASP 2011) defines neuropathic pain 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'.

Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al. 2005). There is often uncertainty regarding the nature and exact location of a lesion or health condition associated with neuropathic pain, particularly in non-specialist settings. Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain, and neuropathic cancer pain (such as, chemotherapy-induced neuropathy, neuropathy secondary to tumour antigens, or caused by direct invasion or compression of neural structures). Examples of conditions that can cause central neuropathic pain include stroke, spinal cord injury and multiple sclerosis. Neuropathic pain can be intermittent or constant, and spontaneous or provoked. Typical descriptions of the pain include terms such as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling, itching and a sensation of pins and needles. People may also describe symptoms of allodynia (pain caused by a stimulus that does not normally provoke pain), hyperalgesia (an increased response to a stimulus that is normally painful), anaesthesia dolorosa (pain felt in an anaesthetic [numb] area or region), and sensory gain or loss (IASP 2011).

A review of the epidemiology of chronic pain found that there is still no accurate estimate available for the population prevalence of neuropathic pain (Smith et al. 2012). For example, the prevalence of neuropathic pain overall has been estimated to be between 6% and 8%, from postal surveys in France (Bouhassira 2008) and the UK (Torrance 2006). However, these estimates came from studies using different questionnaires. Other condition-specific studies have also mirrored the heterogeneous nature of neuropathic pain. For example, painful diabetic neuropathy is estimated to affect between 16% and 26% of people with diabetes (Jensen et al. 2006; Ziegler 2008). Prevalence estimates for post-herpetic neuralgia range from 8% to 19% of people with herpes zoster when defined as pain at 1 month after rash onset, and 8% when defined as pain at 3 months after rash onset (Schmader 2002).

The development of chronic pain after surgery is also fairly common, with estimates of prevalence

ranging from 10% to 50% after many common operations (Shipton 2008). This pain is severe in between 2% and 10% of this subgroup of patients, and many of the clinical features closely resemble those of neuropathic pain (Jung et al. 2004; Mikkelsen et al. 2004; Kehlet et al. 2006). Furthermore, a study of 362,693 computerised records in primary care from the Netherlands estimated the annual incidence of neuropathic pain in the general population to be almost 1% (Dieleman et al. 2008). This considerable variability in estimates of the prevalence and incidence of neuropathic pain and similar conditions from general population studies is likely to be because of differences in the definitions of neuropathic pain, methods of assessment and patient selection (Smith and Torrance 2010, Smith et al. 2012).

A number of pharmacological treatments can be used to manage neuropathic pain outside of specialist pain management services. However, there is considerable variation in how treatment is initiated, the dosages used and the order in which drugs are introduced, whether therapeutic doses are achieved and whether there is correct sequencing of therapeutic classes. A further issue is that a number of commonly used treatments are unlicensed for treating neuropathic pain, which may limit their use. These factors may lead to inadequate pain control, with considerable morbidity.

Commonly used pharmacological treatments include antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs] and serotonin–norepinephrine reuptake inhibitors [SNRIs]), antiepileptic (anticonvulsant) drugs, topical treatments and opioid analgesics. In addition to their potential benefits, all of these drug classes are associated with various adverse effects.

This short clinical guideline aims to improve the care of adults with neuropathic pain by making evidence-based recommendations on the pharmacological management of neuropathic pain outside of specialist pain management services. A further aim is to ensure that people who require specialist assessment and interventions are referred appropriately and in a timely fashion to a specialist pain management service and/or other condition-specific services.

Drug recommendations

For all drugs, recommendations are based on evidence of clinical and cost effectiveness and reflect whether their use for the management of neuropathic pain is a good use of NHS resources. This guideline should be used in conjunction with clinical judgement and decision-making appropriate for the individual patient.

The guideline will assume that prescribers will use a drug's summary of product characteristics (SPC) and the British National Formulary (BNF) to inform decisions made with individual patients

(this includes obtaining information on special warnings, precautions for use, contraindications and adverse effects of pharmacological treatments).

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices (2013). Where recommendations have been made for the use of drugs outside their licensed indications (off-label use), these drugs are marked with a footnote in the recommendations.

Healthcare setting for this guideline

The recommendations in this clinical guideline are for the pharmacological management of neuropathic pain in non-specialist settings only. The Guideline Development Group acknowledged that there are other pharmacological and non-pharmacological treatments that will be of benefit to people with neuropathic pain, within different care pathways in different settings.

The following definitions apply to this guideline.

Non-specialist settings are primary and secondary care services that do not provide specialist pain services. Non-specialist settings include general practice, general community care and hospital care.

Specialist pain services are those that that provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.

More information

You can also see this guideline in the NICE pathway on neuropathic pain.

To find out what NICE has said on topics related to this guideline, see our web page on neuropathic and persistent pain.

See also the guideline committee's discussion and the evidence reviews (in the full guideline), and information about how the guideline was developed, including details of the committee.

1 Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

1.1 List of all recommendations

Key principles of care

1.1.1 When agreeing a treatment plan with the person, take into account their concerns and expectations, and discuss:

- the severity of the pain, and its impact on lifestyle, daily activities (including sleep disturbance) and participation[1]
- the underlying cause of the pain and whether this condition has deteriorated
- why a particular pharmacological treatment is being offered
- the benefits and possible adverse effects of pharmacological treatments, taking into account any physical or psychological problems, and concurrent medications
- the importance of dosage titration and the titration process, providing the person with individualised information and advice
- coping strategies for pain and for possible adverse effects of treatment
- non-pharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist services).

  For more information about involving people in decisions and supporting adherence, see the NICE guideline on medicines adherence.

1.1.2 Consider referring the person to a specialist pain service and/or a condition-specific service[2] at any stage, including at initial presentation and at the regular clinical reviews (see recommendation 1.1.6), if:

- they have severe pain **or**
- their pain significantly limits their lifestyle, daily activities (including sleep disturbance) and participation[1] **or**
- their underlying health condition has deteriorated.

1.1.3 Continue existing treatments for people whose neuropathic pain is already effectively managed, taking into account the need for regular clinical reviews (see recommendation 1.1.6).

1.1.4 When introducing a new treatment, take into account any overlap with the old treatments to avoid deterioration in pain control.

1.1.5 After starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.

1.1.6 Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:

- pain control
- impact on lifestyle, daily activities (including sleep disturbance) and participation[1]
- physical and psychological wellbeing
- adverse effects
- continued need for treatment.

1.1.7 When withdrawing or switching treatment, taper the withdrawal regimen to take account of dosage and any discontinuation symptoms.

Treatment

All neuropathic pain (except trigeminal neuralgia)

1.1.8 Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)[3].

1.1.9 If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

1.1.10 Consider tramadol only if acute rescue therapy is needed (see recommendation 1.1.12 about long-term use).

1.1.11 Consider capsaicin cream[4] for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Treatments that should not be used

1.1.12 Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

- cannabis sativa extract
- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam
- morphine
- oxcarbazepine
- topiramate
- tramadol (this is referring to long-term use; see recommendation 1.1.10 for short-term use)
- venlafaxine

- sodium valproate (follow [MHRA safety advice on sodium valproate]). **[2018]**

Trigeminal neuralgia

1.1.13 Offer carbamazepine as initial treatment for trigeminal neuralgia.

1.1.14 If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.

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[1] The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as 'A person's involvement in a life situation.' It includes the following domains: learning and applying knowledge, general tasks and demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

[2] A condition-specific service is a specialist service that provides treatment for the underlying health condition that is causing neuropathic pain. Examples include neurology, diabetology and oncology services.

[3] Duloxetine is licensed for diabetic peripheral neuropathic pain only, and gabapentin is licensed for peripheral neuropathic pain only, so use for other conditions would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[4] As of 1 April 2019, pregabalin and gabapentin are Class C controlled substances (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 as Schedule 3. Evaluate patients carefully for a history of drug abuse before prescribing and observe patients for development of signs of abuse and dependence (MHRA, Drug Safety Update April 2019).

2 List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

2.1 Monotherapy versus combination therapy for treating neuropathic pain

What is the clinical effectiveness, cost effectiveness and tolerability of pharmacological monotherapy compared with combination therapy for treating neuropathic pain?

Why this is important

Combination therapy is commonly prescribed for neuropathic pain. It may also be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs. However, there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations. Further research should be conducted as described in the table below.

Criterion	Explanation

Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases

	• Spinal cord injury • Trigeminal neuralgia

Intervention(s)	Pharmacological agents as monotherapy or combination therapy. The pharmacological agents include: • Amitriptyline • Clomipramine • Dosulepin (dothiepin) • Doxepin • Imipramine • Lofepramine • Nortriptyline • Trimipramine • Citalopram • Escitalopram • Fluoxetine • Paroxetine • Sertraline • Duloxetine • Mirtazapine • Reboxetine • Trazodone • Venlafaxine • Carbamazepine • Gabapentin • Lacosamide

	• Lamotrigine • Levetiracetam • Oxcarbazepine • Phenytoin • Pregabalin • Valproate • Topiramate • Buprenorphine • Co-codamol • Co-dydramol • Dihydrocodeine • Fentanyl • Morphine • Oxycodone • Oxycodone with naloxone • Tapentadol • Tramadol • Cannabis sativa extract • Flecainide • 5-HT_1-receptor agonists • Topical capsaicin • Topical lidocaine

Comparator(s)	Any of the above listed pharmacological agents as monotherapy compared with any combinations of the above listed pharmacological agents as combination therapy.
Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-point Numerical rating scale [NRS] scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Parallel triple-blinded randomised controlled trial of at least 12-weeks' study period (they should not have enriched enrolment). All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed or should be restricted and maintained at a stable dose in the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications should either not be allowed or, if used, their use should be accurately documented.

2.2 Relationship between symptoms, cause of neuropathic pain and its treatment

Is response to pharmacological treatment predicted more reliably by underlying aetiology or by symptom characteristics?

Why this is important

There is little evidence about whether certain symptoms that present in healthcare settings, or whether different neuropathic pain conditions with different aetiologies, respond differently to different treatments. Current evidence is typically focused on particular conditions and is limited

to particular drugs. Further research should be conducted as described in the table below.

Criterion	Explanation

Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases

	• Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any pharmacological agents as monotherapy or combination therapy (see research recommendation B1).
Comparator(s)	Same pharmacological agents chosen as the main treatments of interest but compare the treatment response across different groups of participants with different neuropathic pain conditions or underlying aetiology.
Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-NRS scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Prospective cohort study All participants should have a 'wash-out' period before assessment for inclusion in the study. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed, or should be restricted and maintained at stable dose during the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications either not be allowed or, if used, their use should be accurately documented.

2.3 Carbamazepine for treating trigeminal neuralgia

What is the clinical and cost effectiveness of carbamazepine as initial treatment for trigeminal neuralgia compared with other pharmacological treatments?

Why this is important

Carbamazepine has been the standard treatment for trigeminal neuralgia since the 1960s. Despite the lack of trial evidence, it is perceived by clinicians to be efficacious. Further research should be conducted as described in the table below.

Criterion	Explanation
Population	Adults with a diagnosis of trigeminal neuralgia.
Intervention(s)	Carbamazepine as monotherapy.

Comparator(s)	Any of the below listed pharmacological agents as monotherapy or combinations. The pharmacological agents include: • Amitriptyline • Clomipramine • Dosulepin (dothiepin) • Doxepin • Imipramine • Lofepramine • Nortriptyline • Trimipramine • Citalopram • Escitalopram • Fluoxetine • Paroxetine • Sertraline • Duloxetine • Mirtazapine • Reboxetine • Trazodone • Venlafaxine • Carbamazepine • Gabapentin • Lacosamide

	• Lamotrigine • Levetiracetam • Oxcarbazepine • Phenytoin • Pregabalin • Valproate • Topiramate • Buprenorphine • Co-codamol • Co-dydramol • Dihydrocodeine • Fentanyl • Morphine • Oxycodone • Oxycodone with naloxone • Tapentadol • Tramadol • Cannabis sativa extract • Flecainide • 5-HT_1-receptor agonists • Topical capsaicin • Topical lidocaine

Outcome(s)	Patient-reported global improvement (on a 7-point scale) Patient-reported improvement in daily physical and emotional functioning including sleep (on a 9-point scale) At least 30% and 50% pain reduction (on a 11-NRS scale) Mean change from baseline pain scores (on a 11-NRS scale) Withdrawal due to adverse effects of the pharmacological agents Adverse effects of the pharmacological agents HRQoL (for example, EQ-5D, WHOQoL- BREF and London Handicap Scale)
Study design	Parallel triple-blinded randomised controlled trial of at least 12 weeks' study period (they should not have enriched enrolment). All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. Baseline pain scores between arms should be equal and clearly documented. Concomitant medications should not be allowed or should be restricted and maintained at a stable dose during the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. Rescue pain medications either not be allowed or, if used, their use should be accurately documented.

2.4 Factors affecting participation and quality of life

What are the key factors, including additional care and support, that influence participation[5] and quality of life in people with neuropathic pain?

Why this is important

There is evidence suggesting that people with neuropathic pain experience poorer physical and mental health than people with other forms of pain, even when adjusted for pain intensity. The discrepancy between pain intensity and quality of life implies that other, unrecognisable factors are important for people with neuropathic pain and that these factors may influence their daily activities and participation. Further research should be conducted as described in the table below.

Criterion	Explanation

Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases

	• Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any important factors, including elements of additional care and support that are perceived as important by adults with neuropathic pain to improve their daily participation.
Comparator(s)	Non-applicable.
Outcome(s)	HRQoL (for example, EQ-5D, WHOQoL- BREF) Measurements of participation (for example, the London Handicap Scale) Satisfaction Patient experiences
Study design	Qualitative research or structured/semi-structured survey questionnaire.

2.5 Impact of drug-related adverse effects on cost effectiveness and quality of life

What is the impact of drug-related adverse effects on health economics and quality of life in neuropathic pain?

Why this is important

Pharmacological agents for neuropathic pain are associated with various adverse effects. However, there is little evidence about how this affects cost of the quality of life of patients receiving treatment. Further research should be conducted as described in the table below.

Criterion	Explanation

Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases

	• Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Comparator(s)	N/A
Outcome(s)	HRQoL (EQ-5D as well as any condition-specific instruments) in people experiencing adverse effects and people experiencing none Resource-use and costs in people experiencing adverse effects and people experiencing none
Study design	Case–control study This research should be performed in a cohort of people receiving a variety of pharmacological treatments for neuropathic pain. Those experiencing adverse effects should be matched with those experiencing none, and their HRQoL and resource-use/costs compared. Matching should be performed using as many modifiers of HRQoL as possible, including age, sex and underlying diagnosis. Analysis of single, named adverse events and also of people experiencing any serious adverse effect (those leading to discontinuation of the medication in question) would be valuable.

2.6 Potential for dependence associated with pharmacological drugs for neuropathic pain

Is there a potential for dependence associated with pharmacological agents for neuropathic pain?

Why this is important

There has been some suggestion that some pharmacological agents for neuropathic pain are associated with increased potential for misuse. However, there had not been enough high-quality evidence to adequately explore this issue. Further research should be conducted as described in the table below.

Criterion	Explanation

Population	Adults with a diagnosis of neuropathic pain. Neuropathic pain conditions include: • Central neuropathic pain/central pain • Complex regional pain syndromes • Compression neuropathies/nerve compression syndromes • Facial neuralgia • HIV-related neuropathy • Mixed neuropathic pain • Multiple sclerosis • Neurogenic pain • Neuropathic cancer pain/cancer pain • Neuropathic pain • Painful diabetic neuropathy/diabetic neuropathy • Peripheral nerve injury • Peripheral nervous system disease/neuropathies • Phantom limb pain • Polyneuropathies • Post-amputation pain • Post-herpetic neuralgia • Post-stroke pain • Post-treatment/post-surgery/post-operative pain • Radiculopathies/radicular pain • Spinal cord diseases

	• Spinal cord injury • Trigeminal neuralgia
Intervention(s)	Any pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Comparator(s)	Any other pharmacological treatment for neuropathic pain, alone or in combination (see research recommendation B1)
Outcome(s)	Drug dependence (including withdrawal symptoms) Drug abuse or drug misuse
Study design	Long-term follow-up from a randomised controlled trial (minimum 6 months) or community-based observational studies. For trials: • Intention to observe dependency and misuse should be made in the study protocol and monitored throughout the study period. • All participants should have a 'wash-out' period after assessment for inclusion in the study and before randomisation. • Baseline pain scores between arms should be equal and clearly documented. • Concomitant medications should not be allowed or should be restricted and maintained at a stable dose in the study. Difference in concomitant pain medication usage at baseline should be clearly described in each trial arm, including details of the number of patients on different drugs. • Rescue pain medications should either not be allowed or, if used, their use should be accurately documented.

[5] The World Health Organization ICF (International Classification of Functioning, Disability and Health) (2001) defines participation as 'A person's involvement in a life situation.' It includes the following domains: learning and applying knowledge, general tasks and demands, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, and social and civil life.

Update information

July 2019: Because of a risk of abuse and dependence, pregabalin and gabapentin are controlled under the Misuse of Drugs Act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3 (as of 1 April 2019). Footnotes in this guideline have been updated to reflect this change.

April 2018: Cautions in the guideline have been added to link to the MHRA's latest advice and resources on sodium valproate. Medicines containing valproate taken in pregnancy can cause malformations in 11% of babies and developmental disorders in 30–40% of children after birth. Valproate treatment must not be used in girls and women including in young girls below the age of puberty, unless alternative treatments are not suitable and unless the terms of the pregnancy prevention programme are met. This programme includes: assessment of patients for the potential of becoming pregnant; pregnancy tests; counselling patients about the risks of valproate treatment; explaining the need for effective contraception throughout treatment; regular (at least annual) reviews of treatment by a specialist, and completion of a risk acknowledgement form. In pregnancy, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation. See the MHRA toolkit to ensure female patients are better informed about the risks of taking valproate during pregnancy.

Minor updates since publication

February 2017: Amended footnote to recommendation 1.1.8 to clarify use of generic pregabalin and off-label status.

October 2015: Title changed from 'Neuropathic pain - pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings' to 'Neuropathic pain in adults: pharmacological management in non-specialist settings' for clarity and consistency with other guidance on this topic.

About this guideline

This guidance is an update of NICE guideline CG96 (published March 2010) and replaces it. Recommendations marked **[2018]** have had a note on sodium valproate added during the April 2018 update.

ISBN: 978-1-4731-0328-3

Accreditation