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PRACTICE

THERAPEUTICS

Drugs for neuropathic pain

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic for this series, please email us at practice@bmj.com.

The patient is a 63 year old freelance editor with type 2 diabetes diagnosed about five years ago that is relatively well controlled with insulin. He has early signs of retinopathy, with normal kidney function and electrocardiogram. Lipid values are normal with diet and atorvastatin 20 mg/day. He developed autonomic and peripheral neuropathy a few months ago, and now experiences postural hypotension and burning pain and clumsiness in his feet. His pain makes concentration and falling asleep difficult. He asks his general practitioner for painkillers to help him continue working.

What drugs are used for neuropathic pain?

Neuropathic pain can have many causes (box 1),[1] with diabetic neuropathy among the commonest. The International Association of the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory system."[2] This article focuses on drugs for treating neuropathic pain, mainly antiepileptics and antidepressants, including those used off-label in the UK (box 2). National Institute for Health and Care Excellence (NICE) guidance[1] recommends offering a choice of amitriptyline, duloxetine, gabapentin, or pregabalin as initial treatment, with switching between these drugs if pain relief is not obtained or the treatment not tolerated.

Successful clinical management requires balancing the benefits and adverse effects of available drugs, lifestyle interventions, and treating the underlying cause if possible. Possible comorbidities (anxiety, depression) need to be considered when choosing the best treatment for an individual patient.

How well do they work?

Evidence for efficacy has been drawn overwhelmingly from Cochrane systematic reviews based on the highest levels of evidence available (box 3).[3] The table⇓ gives the numbers needed to treat (NNTs) for ≥50% reduction in pain intensity over 12 weeks (though with inappropriate imputation for study withdrawal) for duloxetine,[4] gabapentin,[5] lacosamide,[6] and pregabalin.[7] For topical capsaicin the outcome was ≥50% pain intensity reduction over 2-12 weeks.[8]

On current evidence, duloxetine is probably the most effective drug for diabetic neuropathy, and pregabalin for postherpetic neuralgia. The lowest (best) NNTs were 4-6 for duloxetine (60 or 120 mg/day), gabapentin (1200 mg/day), and pregabalin (600 mg/day) for treating diabetic neuropathy; pregabalin (300 and 600 mg/day) for postherpetic neuralgia; and pregabalin (600 mg/day) for central neuropathic pain. However, these NNTs imply a drug specific benefit in only 15-25% of patients, and this might be an overestimate. Most patients do not benefit (but may have adverse events); the distribution of benefit is distinctly bimodal.[3 9 10]

For most off-label drugs (including tricyclic antidepressants such as amitriptyline) there is little or no good evidence of efficacy; existing trials are often unreliable because of small size, short duration, and inadequate outcomes. Cochrane reviews show inadequate evidence of effectiveness for commonly used drugs such as amitriptyline,[9] other tricyclic antidepressants, carbamazepine, 0.075% topical capsaicin, topical lidocaine, and opioids. For treatment of painful diabetic neuropathy, randomised trials of oxcarbazepine were inconclusive, and any small benefit with topiramate was probably artefactual. There is good evidence that lamotrigine is ineffective.[11]

Combination therapies are used—of antidepressant and antiepileptic, or either with opioid—but evidence for effectiveness is weak,[12] and benefits at best modest. There are indications from one small trial that patients with chronic pain

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Box 1: Common conditions that might cause neuropathic pain

Neuropathic pain is defined as peripheral or central depending on the site of injury. The central nervous system is always involved in the processing of pain. Some neuropathic pains may be mixed—that is, they have both peripheral and central components (such as postherpetic neuralgia, post-amputation pain[1]).

Peripheral pain

Common

- Chemotherapy related neuropathies (such as taxanes, vinca alkaloids, platinum compounds)
- Compression neuropathies
- Diabetic polyneuropathy (painful neuropathy in 16% of all diabetic patients, 26% in those with type 2 diabetes)
- HIV related neuropathy
- Idiopathic neuropathies
- Post-surgery neuropathies
- Post-traumatic neuropathies
- Postherpetic neuralgia
- Radiculopathies

Less common

- Hypothyroidism related polyneuropathy
- Uraemia related polyneuropathy

Uncommon

- Arsenic or metronidazole related neuropathy

Central pain

Common

- Post-amputation phantom pain
- Post-stroke pain (central post-stroke pain, which covers stroke and intracranial haemorrhage, incidence 8%)
- Spinal cord injury

Less common

- Multiple sclerosis
- Parkinson's disease

Box 2: Licensed drug treatments available for neuropathic pain in the UK, including those used off-label[1]

Antidepressants (including serotonin–norepinephrine (noradrenaline)reuptake inhibitors)

- Duloxetine (diabetic neuropathy)
- Amitriptyline (not licensed for neuropathic pain)
- Nortriptyline (not licensed for neuropathic pain)
- Venlafaxine (not licensed for neuropathic pain)
- Milnacipran (not licensed for neuropathic pain)

Antiepileptics

- Gabapentin (peripheral neuropathic pain)
- Pregabalin (peripheral and central neuropathic pain)
- Carbamazepine (trigeminal neuralgia)
- Oxcarbazepine (not licensed for neuropathic pain)
- Lamotrigine (not licensed for neuropathic pain)

Topical agents

- Topical capsaicin 0.075% (post-herpetic neuralgia)
- Topical capsaicin 8% (peripheral neuropathic pain in non-diabetic patients)
- Topical lidocaine 5% patch (post-herpetic neuralgia)

who react poorly to one drug may do well with another closely related drug, as with amitriptyline and nortriptyline.[13]

How safe are they?

Serious adverse effects are rare. Carbamazepine is the main cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in people of South East Asian ancestry.[17] Similar concerns are emerging for oxcarbazepine and eslicarbazepine.[18]

Less serious adverse events are common, with somnolence, dizziness, or nausea affecting 15-30% of patients in all drug groups.[7 19] Dry mouth and constipation (10%) are also common (box 4). These often ameliorate over time and can be tolerated. Anticholinergic adverse effects are the main concern when using tricyclic antidepressants even at low doses, particularly in elderly patients (box 4).

Box 3: Evidence standards in trials of drugs for neuropathic pain

Evidence standards for chronic pain have improved dramatically, with outcome, duration, size, and dealing with dropouts all recognised as potential sources of large bias.[3] For example, we now understand:

- Small size in chronic pain trials overestimates treatment effects.[14] For amitriptyline, small trials (<50 patients) produce effectiveness estimates three times better than larger trials (>125 patients).[9]
- Studies shorter than 4-6 weeks overestimate treatment effect.[3]
- When withdrawals due to adverse events are higher with active treatment than with placebo, imputation by "last observation carried forward" (LOCF) leads to major overestimation.[15] When a patient withdraws from treatment (usually due to adverse events or lack of efficacy), the LOCF method uses pain measurements before withdrawal for calculating treatment efficacy. Withdrawals can be 30-60% in chronic pain trials.
- Treatment success is ≥50% reduction in pain intensity over 12 weeks with tolerable adverse events. Patients with chronic pain consider this to be a worthwhile benefit,[10 16] and pain reductions to this extent result in improvements in sleep, fatigue, depression, function, and quality of life.[16]

Box 4: Precautions when prescribing drugs for neuropathic pain[20]

Drug interactions

- Amitriptyline and nortriptyline are substrates of cytochrome P450 2D6—avoid in patients taking fluoxetine, paroxetine, celecoxib.
- Duloxetine has effects on cytochrome P450 2D6 and cytochrome P450 1A2 —avoid in patients taking codeine or tamoxifen.
- Carbamazepine and oxcarbazepine are inducers of cytochrome P450 3A4—avoid in patients taking cytochrome P450 3A4 substrates such as midazolam, oxycodone, sildenafil.
- Pregabalin and gabapentin have no liver metabolism and no known pharmacokinetic drug interactions.

Main adverse effects[20]

Anticholinergic effects—These include dry mouth, postural hypotension, arrhythmias, cognitive impairment, constipation, and urinary retention. These are dose dependent and strongest with amitriptyline, significantly weaker with nortriptyline and non-existent or minimal with tramadol, venlafaxine, duloxetine, carbamazepine, gabapentin, and lamotrigine. For elderly patients, those with prostate hyperplasia, and those for whom constipation or dry mouth is already a problem, consider using lower doses and monitoring closely.

Appetite—Commonly (≥1/100) increased with amitriptyline and pregabalin, whereas it is commonly decreased with duloxetine.

Dizziness—Very common (≥1/10) with carbamazepine, duloxetine, gabapentin, pregabalin, and tramadol and common (1/10) with amitriptyline. Consider using lower doses and monitoring closely in elderly patients and those who already have a problem with dizziness.

Somnolence—Very common (≥1/10) with carbamazepine, duloxetine, gabapentin, and pregabalin and common with amitriptyline.

Nausea—Very common (≥1/10) with carbamazepine, duloxetine, and tramadol.

Cardiovascular effects—Postural hypotension and prolonged QT interval or conduction blocks are common (≥1/100) with antidepressants, more likely with amitriptyline and nortriptyline. Increased blood pressure is common (≥1/100) with duloxetine and gabapentin.

Sexual dysfunction—Common (≥1/100) with all antidepressants, gabapentin, and pregabalin. Anorgasmia is not uncommon in younger men.

Leucopoenia—Very common (≥1/10) with carbamazepine.

Hyponatraemia—Common (≥1/100) carbamazepine and oxcarbazepine.

Serious adverse events

Lamotrigine—Skin reactions occur in about 1 in 10, although serious allergic reactions are rare.

Carbamazepine and oxcarbazepine—Avoid prescribing in people of South East Asian or Japanese origin or in Europeans known to have the HLA-A*3101 allele, as these drugs have been associated with Stevens-Johnson syndrome in these groups (carbamazepine associated with Stevens-Johnson syndrome in 1 in 440 South East Asian people versus about 1 in 3000 Europeans).

Carbamazepine—Hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia in 1/1000 to 1/10 000, usually within 30 days of starting.

Special groups

Elderly people—Start all drugs at lower doses and with slower dose titration. Avoid drugs having anticholinergic effects in patients who have cognitive impairment. Warn patients about dizziness and falls. As duloxetine has no anticholinergic effects, it may be useful in treating elderly patients.

Pregnant women—Tricyclic antidepressants and antiepileptics are not recommended.

Breastfeeding women—Carbamazepine and gabapentin (maximum 2100 mg/day) can be taken. Tricyclic antidepressants should be avoided. There is little information for newer antiepileptics or duloxetine.

How cost effective are they?

Patients with pain intensity reductions of ≥50%, or whose pain is reduced to no worse than mild, record impressive improvements in sleep, fatigue, depression, functioning, and quality of life, with quality adjusted life year (QALY) improvements of 0.1 to 0.2 out of a maximum of 1. Annual drug costs might vary between about £15 for low dose amitriptyline to £830 for high dose pregabalin, making drugs that give good pain relief cost effective, well below the maximum £20 000 per QALY used by NICE. No drug is cost effective without adequate pain relief.

Older drugs such as amitriptyline do not have the same evidence base as newer drugs studied in large randomised trials. However, their low cost, decades of use, and potential efficacy make them important in cost effective treatment of neuropathic pain and beg for modern clinical trials to be performed.

How are they taken and monitored?

Select the drug according to benefits, adverse effects, and comorbidities (see box 4), after discussing these and treatment goals with the patient (see "Tips for patients"). Although current evidence suggests duloxetine may be the most effective drug for diabetic neuropathy, and pregabalin for postherpetic neuralgia and central neuropathic pain, this evidence has limitations. The goal of treatment is major reduction in pain, because sleep, mood, vitality, functioning, ability to work, and

quality of life will improve substantially. Pain measurement is the key; the particular pain scale used is largely irrelevant, but it is important to use the same scale over time. Advise that complete pain relief is unlikely (see "Tips for patients").

NICE guidance for non-specialist settings emphasises the individualisation of treatment[1] but sets no specific pain relief goal. It recommends amitriptyline, gabapentin, duloxetine, or pregabalin as initial therapy for all neuropathic pain conditions except trigeminal neuralgia, with switching between them if pain relief is inadequate or drugs not tolerated. Treatments not to be used include cannabis, capsaicin patch, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and venlafaxine.

All guidance lacks any pragmatic evidence about the order in which drugs might be used for best overall effect in a population. Emerging evidence is that good pain relief develops early and lasts.[21]

Titration of treatment

Titrate the dose to effect and tolerability, monitoring pain relief and adverse effects regularly. Patients often need encouragement to continue with medicines that may make them nauseous or dizzy initially but improve with time, as 2-4 weeks may be needed for effective pain relief. Titration may improve treatment adherence by minimising initial adverse effects and allows doses to be increased to the point where pain relief comes with tolerable adverse effects.

Titrate dose upwards carefully to minimise adverse effects.

Amitriptyline and nortriptyline—Start at 10-25 mg 2 hours before bedtime, increasing dose by 10-25 mg with a week's interval. The usual dose is 50-75 mg 2 hours before bedtime. Sometimes doses up 150 mg are needed.

Duloxetine—Start at 60 mg, although in elderly patients 30 mg is preferred.

Gabapentinoids—Start gabapentin at 300 mg or pregabalin at 75 mg in the evening. In elderly patients, the respective doses can be 100 mg and 25 mg. Pregabalin is administered twice daily, whereas gabapentin needs to be administered three times daily.

Monitoring of treatment

As well as clinical assessment, treatment with carbamazepine or oxcarbazepine may also require monitoring of sodium levels before and every three months in the first year of treatment, and annually thereafter. This is because hyponatraemia (Na^+ <135 but usually >125 mmol/L) is seen in about 20% of patients. It is usually well tolerated and of no importance, but at sodium levels <125 mmol/L symptoms can include fatigue, headache, nausea, muscle cramps (but possibly muscle weakness), or convulsions.

Benefit-risk calculation

The balance between benefit and risk of harm from possible rare serious adverse events depends on the results of titration.

- For patients with good pain relief, improved function and quality of life, and tolerable adverse events, any increased risk from treatment will be offset by large benefits.
- For patients with pain relief but intolerable adverse events, or with trivial pain relief and little improvement in quality of life, stop treatment and try another drug.

What to do when monotherapy fails

Failure to achieve pain relief with any one drug within two to four weeks after titrating to a dose associated with benefit (see table⇓) indicates the need for a trial of another drug, within the same or different class; several trials may be needed for success. Few studies have evaluated combination therapy. For patients who cannot tolerate high doses of a single agent, trying lower doses of two different agents with different adverse effect profiles is worthwhile. Multimodal therapy may give the best results, and drug treatment is often combined with advice to keep as active as possible and make other lifestyle changes. Psychological and physiotherapeutic interventions and stimulation therapies such as transcutaneous electrical nerve stimulation (TENS) are often combined with drug treatments. However, few studies have evaluated combining drug and non-drug therapies.

How do these drugs compare with other therapies?

NSAIDs are often mistakenly used to treat neuropathic pain, but have trivial pharmacological and trial evidence of benefit.[22]

Opioids, including tramadol, are often used for acute management of neuropathic pain, but there is no convincing evidence of benefit over three months or in the longer term using current evidence standards.[23] Opioids are associated with large increases in fracture rates, hospital admission, and all cause mortality in older people compared with propensity matched patients taking NSAIDs.[24]

There is no good evidence supporting the efficacy of non-drug measures (such as acupuncture, homeopathy, TENS) in neuropathic pain.

Case outcome

The patient's general practitioner decided to avoid amitriptyline as the patient had postural hypotension. Gabapentin thrice daily was prescribed as he had been having difficulty sleeping. This produced good pain relief and improved sleep, but daytime sedation and dizziness were problematic. Gabapentin was changed to pregabalin twice daily, which also caused daytime dizziness. This dizziness resolved with a lower morning dose, but daytime pain increased, and so duloxetine was added. Initial nausea with duloxetine disappeared in a few days, and the dose was increased. On both pregabalin and duloxetine, the patient described his pain intensity as mild and he continues to work.

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Tips for patients

- There are no “silver bullets” for treating neuropathic pain. The drugs may be called “painkillers,” but they almost never do that. The aim is to give enough pain control to help you rest and sleep, to work, and to play.
- There is probably a drug or combination of drugs that will work well for you. Many drugs exist for treating neuropathic pain, and your doctor may have to work with you through different drugs or combinations of drugs until you find the treatment that works best for you. The best thing you can do is to be honest about your pain, your functioning, and any adverse effects that bother you. Drug doses will probably be increased or decreased slowly to find the best pain relief while minimising side effects.

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Table

Table 1| Numbers needed to treat (NNTs) for drugs for neuropathic pain conditions from systematic reviews of randomised trials. Values are NNTs (95% confidence intervals)

Drug (daily dose)	Painful diabetic neuropathy	Postherpetic neuralgia	HIV neuropathy	Central neuropathic pain
Antidepressants				
Duloxetine (60 or 120 mg)[4]	5.1 (3.9 to 7.3)	—	—	—
Antiepileptics				
Gabapentin (≥1200 mg)[5]	5.8 (4.3 to 9.0)	7.5 (5.2 to 14)	—	—
Lacosamide (400 mg)[6]	10 (5.2 to 120)	—	—	—
Pregabalin (150 mg)[7]	No benefit	6.9 (4.8 to 13)	—	—
Pregabalin (300 mg)[7]	11 (6.1 to 54)	5.3 (3.9 to 8.1)	—	—
Pregabalin (600 mg)[7]	6.3 (4.6 to 10)	4.0 (3.1 to 5.5)	—	5.6 (3.5 to 14)
Topical capsaicin (8% patch)[8]	—	11 (6.1 to 62)	11 (6.2 to 47)	—

Outcome of ≥50% reduction in pain intensity at 12 weeks using last observation carried forward (LOCF), or ≥50% pain intensity reduction averaged over 2-12 weeks after treatment (capsaicin). Apart from LOCF imputation, which is associated with overestimation of treatment effect in chronic pain trials, these studies met the evidence standards outlined in box 3.

Amitriptyline had no comparable data for individual neuropathic pain conditions, but in five randomised controlled trials (412 patients) in painful diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain had an NNT of 4.9 (3.5 to 8.5).[9] Much larger (worse) NNTs were found for larger studies. Amitriptyline was without effect in post-stroke pain, HIV related neuropathic pain, and cancer related neuropathic pain.