



# Prescribing for neuropathic pain

Learn how treatment guidance from the latest edition of Palliative Care Formulary can support health professionals to manage cancer-related neuropathic pain.

Independent, specialist information, grounded in clinical practice



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# Prescribing for neuropathic pain

Using essential knowledge at the point of care



**Peter is a 52-year-old man with metastatic melanoma who presented to his palliative care clinical nurse specialist with severe pain in his left pelvis and leg. The pain did not respond to additional doses of oral morphine solution taken in addition to his fentanyl transdermal patch.**

The nurse suspected both bone and neuropathic pain components might be contributing to the poor opioid-response and used the Palliative Care Formulary (PCF) Adjuvant analgesics monograph to identify appropriate alternative approaches.

**Medicines Complete** | Adjuvant analgesics

**Neuropathic pain**

Neuropathic pain is caused by multiple mechanisms including:

- overexpression of sodium channels at the site of peripheral nerve injury (see [Anti-epileptics](#))
- overexpression of N-type calcium channels in the spine and brain (see [Gabapentin and pregabalin](#))
- altered postsynaptic excitability (see [Ketamine](#))
- neuro-inflammation in the spine and brain.<sup>14</sup>

First-line adjuvant choices for cancer-related neuropathic pain include [amitriptyline](#), [duloxetine](#), and [gabapentin or pregabalin](#). These are also first-line choices for non-cancer neuropathic pain.<sup>13</sup> Because their efficacy and tolerability are comparable,<sup>15-24</sup> choice is influenced by cost and individual patient circumstances (Table 1). There is increasing interest in relating certain patterns of sensory findings (sensory phenotypic profiling) to the probability of response to particular classes of drug (e.g. [oxcarbazepine](#)).<sup>25</sup>

Drugs that act via different mechanisms can be combined if patients do not respond to a single drug (Figure 2).<sup>3</sup>

<sup>4</sup>In RCTs, opioids at least partly relieved neuropathic pain.<sup>26, 27</sup>

**Step 3**: Amitriptyline and an alternative anti-epileptic, e.g. oxcarbazepine or valproate

**Step 4**: Specialist treatments, e.g. methadone, ketamine, interventional anaesthesia<sup>2</sup>



**PCF Adjuvant analgesics monograph** provides information on drugs that are used for circumstance specific pain that is, or is likely to be, unresponsive to standard treatments.



Following discussion of the treatment options with the palliative care multidisciplinary team and with Peter, pregabalin was prescribed. The nurse consulted the PCF Gabapentin and pregabalin monograph to find the correct starting and typical effective dose of pregabalin for neuropathic pain and decided to start Peter on a dose of pregabalin 25mg PO b.d. because of his frailty, and to titrate up gradually as needed.

Medicines Complete

Gabapentin and pregabalin

Palliative Care Formulary

- Subsections
- Related Content
- Class
- Indications
- Pharmacology
- Cautions
- Drug interactions
- Undesirable effects
- Dose and use
- Supply

### Pregabalin

- start with 75mg PO b.d.
  - if necessary, at intervals of 3-7 days, increase to 150mg b.d. → 225mg b.d. → 300mg b.d. (maximum recommended dose)
- in frail patients
  - start with 25-50mg b.d.
  - if necessary, increase the dose correspondingly cautiously
- typical effective doses:
  - neuropathic pain: 150-300mg b.d.<sup>88</sup>
  - †hiccup: 25-75mg b.d. (see Box A)
  - †hot flushes: 75-150mg b.d.<sup>42</sup>
  - †uraemic itch: 25-75mg after haemodialysis, see [Pruritus, Table 1](#)
  - †spasticity: 150-300mg b.d.<sup>44</sup>
- maximum recommended dose 300mg b.d.

Dose reduction is necessary in renal impairment (Table 4). For patients on HD, the regular dose should be adjusted according to the creatinine clearance and a supplementary single dose given after each dialysis (Table 5); alternatively, some centres time the daily dose post-HD (see [Renal impairment](#)).

Table 4 Pregabalin dose adjustments in renal impairment; modified from SPC

Creatinine clearance (mL/min)	Starting dose	Maximum dose
>60	75mg b.d.	300mg b.d.
31-60	25mg t.d.s. <sup>a</sup>	150mg b.d.
15-30	25-50mg once daily	150mg once daily
<15	25mg once daily	75mg once daily

a. 37.5mg capsules not available, necessitating t.d.s. regimen.

**PCF Gabapentin and pregabalin monograph** provides comprehensive information on the use of gabapentinoids for neuropathic pain including dosing guidance.

Peter's pain responded well to the pregabalin. However, two months later, Peter's condition severely deteriorated. He developed hyperactive delirium and his neuropathic pain returned causing severe distress. He was no longer able to manage oral medication.

The palliative care team considered prescribing ketamine subcutaneously but noted from the PCF Ketamine monograph that this might exacerbate his delirium.



\*Ketamine

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Subsections

Related Content

- Class
- Indications
- Contra-indications:
- Pharmacology
- Cautions
- Drug interactions
- Undesirable effects
- Dose and use
- Supply

## Undesirable effects

Ketamine can be abused or diverted; careful monitoring is essential.

Dose-related psychotomimetic phenomena occur in about 40% of patients with CSCI ketamine; less with PO: euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares, impaired attention, memory and judgement, illusions, hallucinations, altered body image.

Delirium, drowsiness, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting. At higher anaesthetic doses, tonic-clonic movements are very common (>10%) but these have not been reported after PO use or with analgesic parenteral doses.

Erythema and pain at injection site. Upper GI, hepatobiliary, urinary and neuropsychiatric toxicity (Box A).

**Box A** Ketamine and upper GI hepatobiliary, urinary and neuropsychiatric toxicity

Most data concern long-term frequent abusers of large doses of ketamine, generally by nasal insufflation (typically about 3.5g/24h for >3 years). Nonetheless, toxicity has been reported in patients, sometimes after only *days* of use.

The pathophysiology of the toxicity is multifactorial but includes a direct irritant effect of ketamine disrupting the epithelial barrier (e.g. in bladder, GI tract), resulting in inflammation (of tissue, the microvasculature and nerves) and fibrosis; IgE-mediated hypersensitivity may also contribute.<sup>105</sup>

**PCF Ketamine monograph** provides comprehensive information on the specialist use of ketamine in palliative care for pain unresponsive to standard treatments including toxicity risks.

The team discussed the use of clonidine as a useful alternative parenteral option for treating Peter's neuropathic pain and noted from the PCF Clonidine monograph that it may have the added benefit of helping his concurrent hyperactive delirium.

\*Clonidine

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- Indications
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## *†Pain unresponsive to standard treatments<sup>32</sup>*

For opioid poorly-responsive pain, e.g. neuropathic pain, in the setting of a pain crisis and/or a patient in the last weeks of life, particularly if there is concurrent hyperactive delirium:

- give an initial loading/test dose of clonidine 75microgram SC stat; if no benefit, repeat after 1–2h.

If pain does *not* respond, benefit from further doses is unlikely; consider alternatives, e.g. [ketamine](#). If pain improves:

- start clonidine 150microgram/24h CSCI and 75–150microgram SC p.r.n. up to t.d.s.–q.d.s.; if two loading/test doses were required for benefit, start with 300microgram/24h CSCI
- if necessary, increase the CSCI in 150microgram increments every 1–2 days
- half-life prolonged in renal impairment (CrCl <30ml/min); consider halving the above CSCI doses
- typically effective dose 300–600microgram/24h
- maximum reported dose ≤1,500microgram/24h.<sup>55</sup>

Continue prior treatments if partially effective; consider gradual reduction if ineffective or poorly tolerated.

## *†Refractory agitation in the imminently dying<sup>32, 65</sup>*

Generally, clonidine is used SC/CSCI as an alternative to [phenobarbital](#) or when antipsychotics are best avoided, e.g. Parkinson's disease. Follow the same approach as for pain unresponsive to standard treatments.



**PCF Clonidine monograph** provides comprehensive information on the specialist use of clonidine in palliative care for pain unresponsive to standard treatments including use by continuous subcutaneous infusions (CSCI).

Peter was started on clonidine 150microgram/24h by CSCI and prescribed 75microgram SC q8h p.r.n. His pain responded well, and his delirium improved. However, he did report feeling nauseated.

The nurse asked the ward pharmacist whether any anti-emetics could be mixed with clonidine in the same syringe for CSCI. Consulting PCF's Syringe Driver Database through Drug Compatibility Checker, the pharmacist was able to find clinical practice compatibility reports for combinations of clonidine and levomepromazine diluted with sodium chloride 0.9% and combined in a syringe for CSCI over 24h.

Peter's nausea responded well to the addition of levomepromazine to the syringe driver and he died peacefully a few days later.

**Medicines Complete** Drug Compatibility Checker

\*Clonidine

**Clinical practice reports:**

Data from: **Palliative Care Formulary's Syringe Driver Database**

For continuous subcutaneous infusion via a syringe driver in palliative care

5 Appeared Compatible | 0 Incompatible

[See simple results](#)

Compatibility	Drug	Final concentration in syringe	Dose in syringe	Final volume in syringe	Diluent
Compatible	Clonidine Hydrochloride	0.01 mg/mL	0.15 mg	17 mL	Sodium chloride 0.9%
	Levomepromazine Hydrochloride	0.74 mg/mL	12.5 mg		
Compatible	<b>General remarks</b>	<b>Infusion site reaction</b>	<b>Infusion site reaction remarks</b>	<b>Duration</b>	<b>Number of 24 hour periods</b>
	Although the SC site only lasted 24 hours, we concluded that this was due to a reaction to levomepromazine hydrochloride rather than incompatibility because the patient reacted to PRN doses of levomepromazine hydrochloride given thorough	Unknown	-	24 hours	1



**PCF's Syringe Driver Database on Drug Compatibility Checker through MedicinesComplete** contains clinical practice reports on the combination of up to 6 drugs in a syringe for CSCI.



## Palliative Care Formulary

Palliative Care Formulary (PCF) provides unrivalled and expert drug information for health professionals when caring for adult patients facing progressive life-limiting diseases.



## Drug Compatibility Checker

Drug Compatibility Checker through MedicinesComplete supports confident decision making at the point of care. This unique tool combines published data from ASHP Injectable Drug Information with clinical practice reports from Palliative Care Formulary's Syringe Driver Database.

## Access this essential knowledge today

MedicinesComplete makes it easy for health professionals to access essential medicines information at the point of care. Providing trusted evidence-based knowledge for confident decision-making and effective patient care.



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