Guideline Summary

# NICE Opioids in Palliative Care (Clinical Guideline 140) – A Guideline Summary

Penelope J. Teoh[a], Christian F. Camm BA (Hons.)[b]

[a]University of Southampton Medical School; [b]New College, University of Oxford
*Correspondence to:* Penelope J. Teoh, 1 Sirdar Mews, 20 Sirdar Road, Southampton, SO17 3JS
Tel.: +44 7411 551 505; Email: penelopejt@gmail.com

**Article history**
Received: 24 July 2012
Accepted: 28 July 2012
Available online: 2 August 2012

**Provenance and Peer Review**
Commissioned, editorial review

**Keywords**
NICE
Guideline
Policy Review
Palliative Care
Opioids

The following article summarises the recent National Institute of Clinical Evidence (NICE) clinical guidelines for opioid use in palliative care.[1] With the population rapidly ageing, cancer is becoming more common. As such, there is an increasing need to address the pain associated with severe and progressive disease.

The updated NICE guidance (CG 140) targets non-specialists initiating treatment with strong opioids for adults with advanced and progressive disease.[1] It addresses step three of the pain ladder for malignancy according to the World Health Organization pain ladder.[2] It does not address treatment in patients' final days of life or second-line treatment. An adapted pathways is presented in Figure 1.

Professionals should be aware of patients' preferences and needs and aid them in making informed decisions. Informed consent is required and practitioners should refer to the Mental Capacity Act if necessary.

## Recommendations

Patients may have concerns specific to opioid treatment such as addiction, tolerance, and side effects. In addition, opioids are often associated with end-of-life care. Professionals should ask patients about these issues, as they contribute to the unfortunate under-treatment of pain. Addressing such barriers improves compliance and pain control. It is uncommon for cancer patients to become tolerant to the analgesic effects of opioids; increased requirements usually indicate disease progression.[3] However, experience enables professionals to identify pseudo-addiction behaviour and written information will improve a patient's trust in their doctor.[4] Similarly, addiction is a rare occurrence and concerns should not prevent adequate pain relief. The International Association for Hospice and Palliative Care suggests that practitioners should not avoid administering opioids due to concerns over psychological dependence.[3]

Patients require information to be accessible (in their native language if necessary). It must be culturally appropriate and tailored to their needs. Delivery of such information should be both written and verbal. Families and carers can also be included in decision-making if the patient prefers this.

When prescribing strong opioids, professionals should inform patients of:

- When and why strong opioids are used to treat pain.
- How effective they might be.
- Potential opioid side effects.
- Possible signs of opioid toxicity.
- Appropriate storage of medications.
- Follow-up or future prescriptions.
- Contact details for advice out of hours (patients can also refer to the British Pain Society's patient publications).[5]

For background and breakthrough pain:

- How, when, and how regularly medication should be taken.
- Duration of pain relief that can be expected.

## Titrating the dose

Historically, morphine has been the drug of choice due to low cost and availability. Two systematic reviews collating nine randomised trials have supported the administration of morphine over common alternatives oxycodone and hydromorphone.[6,7] These drugs can be easily administered orally by crushing, or in a liquid form, and provide similar pain relief and side effects. However, morphine is still considered a reference drug.[6]

When initiating treatment, one should give oral sustained-release (SR) or oral immediate-release (IR) morphine (e.g. 10–15 mg 12-hourly = total of 20–30 mg/day), depending

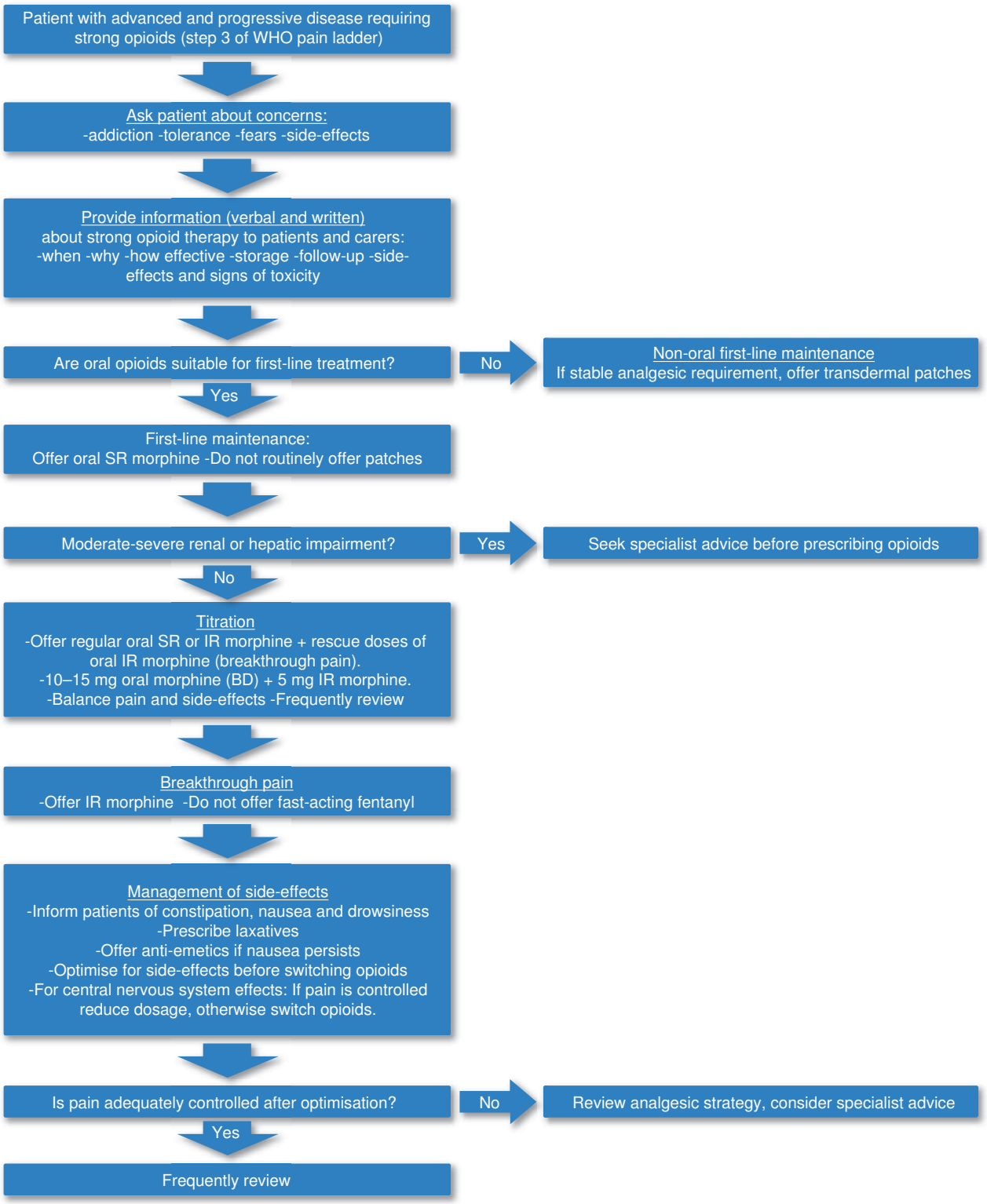


**Fig 1** Opioid pathway (adapted from NICE guideline CG 140).[1]

upon patient preference. Although IR oral morphine allows more rapid titration, one randomised controlled trial did not show a significant difference between IR and SR oral morphine.[8] Another demonstrated that intravenous morphine controls pain more quickly than oral morphine; however, this is often unsuitable in the community.[9]

Oral IR morphine is first-line rescue treatment for such pain in patients on maintenance oral morphine treatment. Patients should be offered rescue doses of 5mg for breakthrough pain. The European Association for Palliative Care (EAPC) recommends one-sixth of the total 24-hr dose.[10] For patients with renal or hepatic co-morbidities one should seek specialist advice. As dosage cannot be estimated, patients should be reviewed frequently and adjust dosage to optimise pain relief and side effects. Fast-acting fentanyl should not be offered. Disease progression may worsen pain; therefore, practitioners should frequently review patients.

**Table 1** The equivalence of transdermal patches in oral morphine

| Transdermal Patch (micrograms) | Equivalent of oral morphine (milligrams/day) |
|---|---|
| Fentanyl 12 | 45 |
| Buprenorphine 20 | 30 |

## First-line maintenance

Oral sustained-release morphine should be offered. If unsuitable and analgesic requirements are stable, one should consider transdermal patches, appreciating that a conversion must be made when prescribing the new medication (Table 1). They may be beneficial in patients who cannot swallow.

Low quality trials, with both poor methodology and lack of blinding, suggest similar efficacy of oral morphine and transdermal patches. However, transdermal patches are associated with less constipation and patients often favour this route of administration.[10,11]

Alternatively, if analgesic requirements are unstable, subcutaneous opioids can be considered. Treatment with the lowest acquisition cost in both patch and subcutaneous delivery should be used.

Methadone is not recommended within the guidelines. It demonstrated similar efficacy to morphine in three randomised controlled trials (RCTs).[12–14] However, one RCT showed an association with more central nervous system effects (sedation).[13] Methadone also has a lengthy, unpredictable half-life; therefore, it should be administered with caution.

## Management of side effects

### 1. Management of constipation

Patients should be informed of the side effects that they may experience, including constipation, nausea, and drowsiness.

All patients should be prescribed prophylactic laxatives for probable constipation. There are various drugs from which to choose and a systematic review demonstrated no difference between them.[15] Using several laxatives with differing mechanisms may be beneficial for resistant constipation. The British National Formulary suggests co-danthramer or lactulose solution with a senna preparation to be administered regularly.[16] Co-danthramer is only to be used in terminal patients due to carcinogenic effects.[17] When other laxatives exert no effect, subcutaneous methylnaltrexone may be of clinical benefit and is cost-effective, and therefore, is recommended by EAPC.[17,18]

### 2. Management of nausea

Not all patients experience nausea, however, if it occurs it usually resolves in several days.[19] Offer anti-emetics for nausea persisting past initial phases of opioid treatment. Two RCTs demonstrate that metoclopramide alleviates nausea. However, opioid switching, altered route of administration, and reduced dose may alleviate nausea.

### 3. Management of drowsiness

Drowsiness or sedation often resolves in a few days. Patients should be aware of its detrimental effect on driving and other tasks. Dose reduction, if pain is controlled, can ameliorate central nervous system side effects.

With each side effect, optimise therapy before considering the switch of opioids. Switching opioids may aid uncontrolled pain and unmanageable side effects such as nausea. However, neither a Cochrane review nor others have been able to find sufficient, high quality evidence supportive of opioid switching.[20,21]

## Switching opioids

Switching opioids may be indicated in patients with uncontrolled pain or unacceptable side effects. Dose conversion ratios vary (Table 2); however, starting doses after switching should be lower than the equivalent original opioid.[22]

## Alternative routes

### 1. Intravenous and subcutaneous

Intravenous opioids relieve pain more quickly than subcutaneous opioids. They can relieve pain within 1 hour and are generally used for severe, unrelieved, pain.[9] In contrast, IR oral morphine exerts an effect in 20 minutes but requires administration every 4 hours.[23] Subcutaneous injections are first-line for patients unable to swallow or use a transdermal patch. Both routes require the same dose and are equally tolerated.[7,21,24,25]

**Table 2** Relative analgesic ratios for opioid switching[18]

| Drug switch | Relative analgesic ratio | Strength of the recommendation for use | Dose if the patient is on 60 mg/day oral morphine |
|---|---|---|---|
| Oral morphine to oral oxycodone | 1:1.5 | Strong | 3.75 mg/h (equivalent to 90 mg per 24 h) |
| Oral oxycodone to oral hydromorphone | 1:4 | Strong | 10 mg/h (equivalent to 240 mg per 24 h) |
| Oral morphine to oral hydromorphone | 1:5 | Weak | 12.5 mg/h (equivalent to 300 mg per 24 h) |
| Oral morphine to TD buprenorphine | 75:1 | Weak | 35 µg/h (equivalent to 0.8 mg per 24 h) |
| Oral morphine to transdermal fentanyl | 100:1 | Strong | 25 µg/h (equivalent to 0.6 mg per 24 h) |

### 2. Rectal

Rectal morphine relieves pain as well as intravenous and subcutaneous administration but with a faster onset; however, this route is unacceptable to some patients.[24]

### 3. Epidural

Epidural administration had similar efficacy to oral and subcutaneous morphine in nine low-quality RCTs.[26] Although potentially dangerous complications can occur, such as CSF leak, spinal administration can benefit patients with severe side effects or insufficient pain control.

## Patients with renal failure

A systematic review yielded low quality studies with a lack of clear evidence, thus professionals should use caution when prescribing opioids in patients with renal failure.[27] Low dose subcutaneous or intravenous fentanyl or buprenorphine can be administered, however, dose reduction of morphine may be an alternative. If in doubt, contact the local palliative care team.[28]

## Paracetamol and NSAIDs

The current NICE guidelines do not cover this aspect of care. However, in three studies, combining paracetamol with NSAIDs was shown to increase pain relief and reduce opioid dose. Unfortunately, paracetamol increased the prevalence of gastrointestinal side effects in one study.[18] These studies failed to use a heterogeneous population due to differing drug dosages and routes of administration. Furthermore, they did not include long-term evaluation; the longest period of follow-up was 12 weeks. As usage is associated with severe side effects, especially in the elderly, recent EPAC recommendations suggest professionals should use paracetamol with caution.[18]

## Antidepressants and anticonvulsants for neuropathic pain

Two RCTs demonstrated that adding antidepressants or anticonvulsants as adjuvants to opioids relieves pain more than opioids individually.[29] However, use of such drugs (e.g. gabapentin and amitriptyline) may elicit CNS side effects.

## Conclusions

After discussions regarding a patient's concerns and the nature of their proposed care, first-line treatment of SR or IR morphine should be administered orally. Clinicians should not withhold opioids over concerns of psychological dependence. However, they should monitor the patient for side effects. In particular, constipation, nausea, and drowsiness are common. Prophylactic laxatives should be prescribed and treatment for nausea or drowsiness can be initiated if symptoms persist. Caution should be taken when prescribing to patients with renal impairment. If pain remains uncontrolled or side effects are intolerable, one can consider opioid switching.

### *Ethical approval*

No ethical approval required for this paper.

### *Conflict of interest*

No conflicts of interest have been declared by the authors.

### *Author contribution*

PJT: Writing, Critical Revision, Final Approval.
CFC: Concept, Critical Revision, Final Approval.

### *Funding*

No funding source declared by authors.

1 NICE. Clinical Guidance CG140. http://publications.nice.org.uk/opioids-in-palliative-care-safe-and-effective-prescribing-of-strong-opioids-for-pain-in-palliative-cg140 (accessed 10th July 2012).
2 World Health Organisation. WHO's Pain Ladder. http://www.who.int/cancer/palliative/pain-ladder/en/ (accessed 10th July 2012).
3 International Association for Hospice and Palliative Care. Pain. http://www.hospicecare.com/manual/pain3.html (accessed 11th July 2012).
4 Breivik H. Opioids in cancer and chronic non-cancer pain therapy- indications and controversies. Acta Anaesthesiologica Scandinavica. 2001;45(9):1059–66.
5 The British Pain Society. Managing cancer pain: information for patients. http://www.britishpainsociety.org/book_cancer_pain_patients.pdf (accessed 17th July 2012).
6 Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. Palliat Med, 2011;25:402–9.
7 Wiffen PF, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev, 2007; 4:CD003868.
8 Klepstad P, Kaasa A, Jystad A, Hval B, Borchgrevink PC. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. Pain, 2003;101:193–8.
9 JHarris JT, Kumar KS, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med, 2003;17:248–56.
10 Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: A systematic review undertaken as part of an EPCR opioid guidelines project. Palliat Med, 2011;25: 5516–24.
11 Tassinari D, Sartori S, Tamburini E, et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. J Palliat Med, 11 (2008), pp. 492–501.
12 Mercadante S, Porzio G, Ferrera P, Fulfaro F, Verna L, Villari P, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain, 2008;12:1040–6.
13 Bruera E, Palmer JL, Bosnjak S, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol, 2004;22:185–92.
14 Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manage, 1986;1:203–7.
15 Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane Database Syst Rev, 2011;1:CD003448.
16 Joint Formulary Committee. British National Formulary. 60 ed. London: BMJ Group and Pharmaceutical Press, 2010.
17 Ahmedzai SH, Boland J. Constipation in people prescribed opioids http://bestpractice.bmj.com/best-practice/evidence/intervention/2407/0/sr-2407-i5.html (accessed 18th July 2012).
18 Caraceni A, Hanks G, Kaasa S, et al. for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC), Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC, The Lancet Oncology, 2012;13(2):e58–e68.
19 Earhaw SR, Klok RM, Iyer S, McDade C. Methylnatrexone bromide for treatment of opioid-induced constipation in patients with advanced illness – a cost-effectiveness analysis. Aliment Pharmacol Ther. 2010;8:911–21.
20 Schisler RE,Groninger H, Rosielle DA. #248 Counseling Patients on Side Effects and Driving When Starting Opioids. http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_248.htm (Accessed 18th July 2012).
21 Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev, 2004;3:CD004847.
22 Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review. Palliat Med, 2011;25:494–503.
23 NHS Evidence. Palliative cancer care- Pain- Management: Initiating and titrating Morphine http://www.cks.nhs.uk/palliative_cancer_care_pain/management/quick_answers/scenario_managing_pain_non_emergency/initiating_and_titrating_morphine (Accessed 18th July 2012).
24 Radbruch L, Trottenberg P, Elsner F, Kaasa S, Caraceni A. Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: an EPCRC opioid guidelines project. Palliat Med, 2011;25:578–96.
25 Anderson SL, Shreve ST. Continuous subcutaneous infusion of opiates at end-of-life. Ann Pharmacother, 2004;38:1015–23.
26 Kurita GP, Kaasa S, Sjogren P. European Palliative Care Research Collaborative (EPCRC). Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative

Care Research Collaborative (EPCRC) opioid guidelines project. Palliat Med, 2011;25:560–77.
27 King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med, 2011;25:525–52.
28 NHS. WAHT End of life care- Quick reference guide http://education.worcestershire.nhs.uk/files/General/End%20of%20Life%20Care%20Quick%20Reference%20Card%20A4.pdf (Accessed 18th July 2012).
29 Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med, 2011;25:539–53.