Cancer Council Australia

Cancer pain management in adults

Guideline developer:

Australian Adult Cancer Pain Management Guideline Working Party

1 Introduction

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1.1 Introduction

1.1.1 Scope of this guideline

This guideline provides brief, point-of-care recommendations for screening, assessment and management of cancer-related pain in adults. It focuses on chronic pain rather than acute pain caused by cancer treatments or pain in cancer survivors (which is best addressed by referral to a specialist pain medicine physicians). Future work is planned to develop guidelines for management of acute pain in people with cancer.

The current guideline includes recommendations on pharmacological and non-pharmacological management and patient awareness and self-management in adults. It should not be used as a guide to pain management in children with cancer.

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1.1.2 Who this guideline is intended for

This guideline is intended for Australian health professionals of all disciplines caring for people with cancer. These recommendations are not intended to replace expert clinical judgment, but to enable those without specialist knowledge to provide the essentials of care.

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1.1.3 Background

An estimated 30–75% of people with cancer experience pain, and pain is under-treated in up to half of cases.[1][2][3][4][5] Failure to manage pain is due to barriers at all levels - patient, caregiver, health professional and healthcare system. [6][7][8][9][10][11][12][13][14]. The first guideline to focus on management of cancer pain was released by the World Health Organisation in 1986.[15] Since then, a large number of guidelines have become available internationally. Implementation of evidence-based clinical practice guidelines for cancer pain can improve the processes of care and patient outcomes.[10]

1.1.4 The need for an Australian guideline

The management of cancer pain in Australia has been identified as an important area for improvement by both the National Institute of Clinical Studies (National Health and Medical Research Council) and the Cancer Institute New South Wales.[16][17] Timely access to best-practice, evidence-based assessment and care for patients in pain is one of six major goals identified by the Australian National Pain Strategy, [18] which was developed by clinicians and consumers at the 2010 National Pain Summit.[19] The National Pain Summit's Cancer Pain and Palliative Care Working Group recommended that promotion of pain management guidelines and systems to ensure adequate assessment and management of cancer pain should be primary objectives. As a starting point, the Cancer Pain and Palliative Care Working Group determined that existing international and overseas guidelines should be adapted for Australian clinical practice.

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1.1.5 Development of this guideline

An Organising Committee (Table 1) was formed in October 2010 to plan and oversee development of this guideline. To better understand clinician needs, a national survey of current practice was administered online from August 2011 to April 2012. Five hundred and twenty seven health professionals responded from a wide range of disciplines. Respondents were strongly supportive of Australian guidelines and implementation strategies but advocated for these to make use of existing international guidelines rather than be developed de novo.[20] The Organising Committee decided to adapt international guidelines to the Australian setting using the ADAPTE approach.[21] ADAPTE specifies that guideline adaptation follow a three phase process of Set-up, Adaptation and Finalization.

During Set-up, the Organising Committee agreed that synthesis and adaptation would likely be required across a number of guidelines rather a single candidate and decided to convene a Working Group to provide expert guidance (Table 2). The Working Group held its inaugural meeting in January 2012. Meetings were held on a bi-monthly basis. A conflict of interest declaration was signed by each member. Two panels of expert clinicians (Table 3) individually provided expert consultation to the Working Group on pharmacological management and management of adverse effects.

During the Adaptation phase, discussions were initially aimed at more clearly defining the focal Population, Intervention, Professionals, Outcomes and Health setting for the adapted guideline (PIPOH). Existing guidelines were sought via the reference lists of previous reviews.[22][23][24] and searches of online databases and clearing houses identified by the ADAPTE manual. Guidelines were screened according to the following eight criteria: 1) a primary focus on adults with chronic cancer pain; 2) relevance across tumour types and stages; 3) providing recommendations for assessment and/or management of pain by means of either pharmacological or non-pharmacological intervention; 4) capacity to inform pain assessment and management across disciplines and settings; 5) published in the previous 3 years (i.e. 2008 or later); 6) national or international (i.e., not centre-specific); 7) available in English; and 8) independently rated as 'recommended' or 'strongly recommended' by two members of the Working Group based on criteria of the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument.[21] These eight criteria resulted in the following guidelines being considered for adaptation:

- Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline [Version amended 18 July 2011] Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk/pdf/SIGN106.pdf
- NHS Quality Improvement Scotland. Best practice statement. The management of pain in patients with cancer. Edinburgh: NHS Quality Improvement Scotland; 2009. Available from: http://www.palliativecareguidelines.scot.nhs.uk/documents/PAINCANCERREV_BPS_NOV09.pdf
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. Version 1.2012: NCCN; 2012. Available from: http://www.nccn.org
- Ripamonti CI, Bandieri E, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol 2011; 22(Suppl 6): vi69-vi67. Available from: http://annonc.oxfordjournals.org/content/22/suppl_6/vi69.long

- Caraceni A, Hanks G, Kaasa S, European Palliative Care Research Collaborative. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations for the EAPC. Lancet Oncol 2012; 13: e58-e68. Web version available from: http://www.eapcnet.eu/LinkClick.aspx?fileticket=i-bB4cvZyzg%3d&tabid=1794 and associated reviews.[25][26][27][28][29][30][31][32][33][34][35][36][37][38][39]
- National Institute of Clinical Excellence Guideline Development Group. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. NICE clinical guideline 140. Manchester: NICE; 2012. Available from: http://www.nice.org.uk/nicemedia/live/13745/59285/59285.pdf *

The Working Group compared recommendations in the source guidelines and assessed them according to currency, quality of evidence on which they were based, and applicability to the Australian setting. Recommendations identified as the most suitable were either directly adopted or modified.

In clinical situations for which no recommendation applicable to the Australian setting was available, the Working Group developed recommendations based on members' clinical expertise and experience. Recommendations of this kind are distinguished from those adapted from existing guidelines by the term 'Consensus'.

Recommendations for pharmacological pain management and recommendations for management of adverse effects were referred to two panels of expert clinicians (Table 3).

For each of the recommendations in this Australia guideline, we cite as sources:

- one or more adapted guidelines. To see the grade of each recommendation within its source guideline (where applicable), or the level of evidence on which recommendations are based, users should refer to the original guidelines (links provided).
- other Australian authorities
- the considerations of our Working Group and panels of Australian expert clinicians (for any recommendations for which a quality evidence-based recommendation in a source guideline could not be identified).

Where available, we refer readers to other Australian clinical practice guidelines for the management of specific clinical problems (e.g. psychosocial concerns).

Table 1. The Australian Adult Cancer Pain Management Organising Committee

Patricia Davidson (Co-chair)	Nurse Director, Centre for Cardiovascular and Chronic Care, University of Technology Sydney (UTS) Professor of Cardiovascular Research, St Vincent's Hospital, Sydney	Sydney, NSW
Melanie Lovell (Co-chair)	Palliative care physician Staff Specialist, Palliative Medicine, Greenwich Hospital Visiting Medical Office, Mater Hospital Clinical Senior Lecturer, Northern Clinical School, The University of Sydney	Sydney, NSW

Meera Agar	Palliative care physician Director of Palliative Care, Braeside Hospital Conjoint Associate Professor, South Western Sydney Clinical School, University of New South Wales (UNSW) Conjoint Associate Professor, School of Medicine, The University of Notre Dame, Australia Director of Clinical Trials, Ingham Institute of Applied Medical Research	Sydney, NSW
Anna Green (Administrative support)	Research Administrative Coordinator, Centre for Cardiovascular and Chronic Care, UTS	Sydney, NSW
Tim Luckett (Project Manager)	Program Coordinator, Improving Palliative Care through Clinical Trials (ImPaCCT) Research Fellow, Faculty of Health, UTS and South Western Sydney Clinical School, UNSW	Sydney, NSW

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Table 2. The Australian Adult Cancer Pain Management Working Group

Melanie Lovell (Chair)	Palliative care physician Staff Specialist, Palliative Medicine, Greenwich Hospital Visiting Medical Office, Mater Hospital Clinical Senior Lecturer, Northern Clinical School	Sydney, NSW	No conflict of interest (COI)
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	Medical oncologist		

Frances Boyle	Director, The Patricia Ritchie Centre for Cancer Care and Research, The Mater Hospital North Sydney. Professor of Medical Oncology, Northern Clinical School, The University of Sydney Honorary Medical Officer, Royal North Shore and Greenwich Hospitals, Sydney Visiting Medical Oncologist, North Shore Private Hospital, Sydney Medical Oncologist, Melanoma Institute of Australia Medical Director, Pam McLean Centre, The University of Sydney	Sydney, NSW	Member of Advisory Board for Takeda Pharmaceuticals Australia Pty Ltd
Tim Luckett (Coordination and administrative support)	Program Coordinator, Improving Palliative Care through Clinical Trials (ImPaCCT) Research Fellow, Faculty of Health, UTS Research Associate, South Western Sydney Clinical School, UNSW	Sydney, NSW	No COI
Jane Phillips	Nurse Professor Palliative Nursing, School of Nursing, The Cunningham Centre for Palliative Care and The University of Notre Dame, Australia	Sydney, NSW	No COI
John Stubbs	Consumer Cancer Voices Australia (until June 2012) canSpeak (July 2012 onwards)	Sydney, NSW	No COI

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Table 3. Expert panels of clinicians who provided consultation to the Working Group

Pharmacological management panel		
David Currow	Palliative care physician Professor and Chair of Palliative and Supportive Services, Flinders University Chief Cancer Officer and Chief Executive Officer, the Cancer Institute NSW	Adelaide, South Australia

Jan Maree Davis	Director of Palliative Care, St George Hospital President, NSW Society of Palliative Medicine Senior Research Fellow, Faculty of Medicine, UNSW	Sydney, NSW
Janet Hardy	Palliative care physician Director of Palliative and Supportive Care, Mater Health Services Brisbane	Brisbane, Queensland
Christine Sanderson	Palliative care physician Staff Specialist, Palliative Medicine, Calvary Health Care Sydney Research Fellow, Palliative and Supportive Services, Flinders University	Sydney, NSW
Odette Spruyt	Palliative care physician Director of Pain and Palliative Care, Peter MacCallum Cancer Centre	Melbourne, Victoria
Management of adverse effects panel		
Melanie Benson	Palliative care physician Staff Specialist, Palliative Medicine, The Alfred	Melbourne, Victoria
Katherine Clark	Palliative care physician Director and Area Director of Palliative Care, Calvary Mater Newcastle Conjoint Professor, School of Medicine and Public Health, The University of Newcastle	Newcastle, NSW
Winston Liauw	Medical oncologist Clinical pharmacologist Staff Specialist, Medical Oncology, St George Cancer Care Centre Sydney Conjoint Associate Professor, Faculty of Medicine, UNSW Chair, Chair Cancer Institute NSW Clinical Research Ethics Committee Member of the Board, National Prescribing Service Visiting Medical Officer, Southern Oncology Specialists and St George Private Hospital	Sydney, NSW

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1.1.6 Funding

Development of this guideline was funded by Improving Palliative Care through Clinical Trials (ImPaCCT) and HammondCare.

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1.1.7 Updating the guideline

This guideline will be updated each year from 2013 to include recommendations added to new editions of the source guidelines or any new guidelines that meet criteria for quality and applicability.

The developers of this guideline acknowledge that the recommendations in the first edition may not fully meet the information needs of Australian clinicians. Users are invited to use the blue buttons to submit clinical questions for consideration in the next edition. Selected clinical questions will be answered by systematic reviews or new Australian research.

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1.1.8 Acknowledgements

Jutta von Dincklage, Product Manager (Wiki Development), Cancer Council Australia

Jenni Harman, Medical writer, Meducation Australia

painaustralia (http://www.painaustralia.org.au)

The Working Group thanks Cancer Council Australia for hosting the online consultation draft of this guideline on their website.

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1.3 Notes

* ↑ NICE 2012 became available just as a draft of recommendations based on the other five guidelines was being finalised. Draft adapted recommendations for opioid use were checked against those of the NICE guideline for consistency.

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2 Summary of recommendations

2.1 Summary of recommendations

2.2 Cancer pain management in adults: Evidence-based clinical practice guidelines adapted for use in Australia

2.2.1 Patient-centred care

Recommendation
PCC1. Routinely establish a multidisciplinary team approach to pain management that involves allied care health professionals and primary care health professionals according to the person's pain management needs and preferences. (SIGN)
PCC2. Adopt a person-centred approach to pain management (NICE), which involves: ■ taking into account the patient's needs and preferences ■ enabling the person to make informed decisions about their care and treatment ■ providing culturally appropriate care and information ■ involving the person's partner, carer or family in treatment decisions, if the person wishes.

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2.2.2 Screening

Recommendation
S1. For all patients who are able to communicate their level of pain: At each clinical encounter, assess worst and average pain intensity during the previous 24 hours using a self-reported numerical rating scale from zero to 10, where zero represents 'no pain' and 10 represents 'worst pain you can imagine'. (NCCN)
S2. For people who cannot self-report due to cognitive impairment: At each clinical encounter, use the Abbey Pain Scale. (Consensus) Recommended by the Australian Pain Society: Australian Pain Society. Residential Aged Care Facilities - Management Strategies. Sydney: Australian Pain Society; 2005. Available from: http://www.apsoc.org.au/owner/files/9e2c2n.pdf APS 2005.

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2.2.3 Assessment

Recommendation
A1. Complete a comprehensive assessment if either of the following apply: • a new patient reports a pain score of 2 or more on self-reported numerical rating scale of zero to 10 or pain score is 3 or more on the Abbey Pain Scale (see Screening) • an existing patient reports a new pain or a sudden, unexpected change in intensity of pain. (Consensus) Assess all the following to determine the individual's pain management needs: • Disease status and treatment (Consensus) The Working Group considered this information to provide necessary context for other assessments • Pain severity (using a validated tool) (NCCN, SIGN) • Pain experience (location, interference, timing, description, aggravating and relieving factors) (ESMO, NCCN, NHS, SIGN) • Current and previous management of pain (ESMO, NCCN, NHS, SIGN) and other symptoms (Consensus) • Pain meaning for the person and their beliefs and knowledge (NCCN, NHS, SIGN), including concern about pain and its treatment (e.g. perceived addictiveness of opioids) (NICE) • Psychosocial status (ESMO, NCCN, NHS, SIGN), including risk factors for opioid misuse (NCCN) • Cognitive functioning (Consensus) The Working Group considered this information to provide necessary context for other assessments • Physical examination and, where needed, further investigations (NCCN, NHS, SIGN) • Functional status (ESMO) • Risk factors for poorly controlled pain (NCCN) • Patient and family preferences (goals and expectations for comfort, advance directives) (NCCN) • Factors suggesting an oncological emergency. (NCCN) Reassess whenever there is a change in pain or a new pain is reported.

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2.2.4 Education

Recommendation
SM1. For all patients with pain, provide education about cancer-related pain and its management. (NCCN, SIGN)
SM2. Patients with pain should be provided with verbal and written information on pain and its management, including the following: • pain causes • common experiences of cancer pain (e.g. onset, timing) • effective treatments (including medicines and non-pharmacological management strategies) • effect of medicines including breakthrough analgesia (e.g. onset and duration of effect; when to take them) • side-effects of medicines such as opioid-related constipation and how to prevent or manage them • any safety concerns (e.g. mixing with alcohol, driving) • ways to ensure patients have adequate access and supply to prescribed opioids • how to work with health professionals to achieve the best pain control possible (e.g. the importance of reporting rather than concealing pain, side-effects and other concerns about medication) • common attitudes and beliefs that may prevent people with cancer receiving effective pain control (e.g. fears that opioids are addictive and used only at the end of life, and that patients will develop tolerance over time requiring dose escalation) • when to seek help (e.g. if vomiting and unable to keep down fluids for one day, bowels not open 3 days, new pain, change in pain or pain not relieved by medication, difficulty arousing the patient from sleep easily during the daytime, confusion, difficulty accessing the medications). (Consensus) Systematic review by Koller et al (2012): Koller A, Miaskowski C, De Geest S, Opitz O, Spichiger E. A systematic evaluation of content, structure, and efficacy of interventions to improve patients' self-management of cancer pain. J Pain Symptom Manage. 2012 Aug;44(2):264-84.
SM3. Include the person’s family, carers and significant others in education about pain and its management, if appropriate. (Consensus) Carers are frequently involved in decision-making (e.g. to start and adhere to opioids) and management

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2.2.5 Pharmacological management

Recommendation
P1. For patients with continuing pain, begin regular analgesia with paracetamol or a nonsteroidal anti-inflammatory drug (NSAID). (ESMO, NCCN, SIGN)
P2. If pain continues despite treatment with paracetamol or NSAIDs, consider regular oral opioids. For patients with normal renal and hepatic function, start with a low dose (e.g. morphine 20–30 mg per day (10–15 mg bd or 5 mg q4h) with 5 mg rescue doses as needed for breakthrough pain. (ESMO, NCCN, SIGN)
P3. If pain continues or recurs despite regular oral opioid analgesia and the patient feels that analgesia is inadequate, consider either of the following options: • Add a NSAID (if the person is not already taking and NSAID and has no contraindications). (EAPC) Read note Weak evidence that the addition of NSAID to WHO Step III opoiods can improve analgesia or reduce opioid does requirement • Increase the regular dose to incorporate the rescue doses (SIGN), then reassess pain severity and adverse effects within 48 hours. (Consensus) Sample calculation A patient taking 5 mg morphine q4h requires three extra 5 mg rescue doses for breakthrough pain. The resulting total 24-hour dose is 45 mg morphine. The new regular analgesic regimen is morphine 7.5 mg q4h, with a new rescue dose of 7.5 mg.
P4. Methadone should be prescribed and titrated only by specialists familiar with its use. (EAPC, ESMO, NCCN)
P5. The transdermal route of administration can be considered as an alternative to oral administration if required, for reduced risk of constipation or patient convenience. (EAPC) Use one of the following options: • Switch to transdermal fentanyl. Note: A 12 mcg fentanyl transdermal patch is equivalent to 45 mg morphine daily. (NICE) • Switch to transdermal buprenorphine (suitable for patients with stable mild pain only). Note: A 20 mcg buprenorphine transdermal patch is equivalent to 30 mg morphine daily. (NICE) Due to long duration of action, the transdermal route should be considered only when pain is stable. (ESMO, NCCN, SIGN)

Recommendation
P6. In addition to regular opioids, routinely prescribe short-acting analgesia at a dose equivalent to one-sixth of total 24-hour dose, to be administered if breakthrough pain occurs. (NHS, SIGN)
P7. If breakthrough pain occurs, re-titrate the regular opioid 24-hour dose. (SIGN)
P8. If the person experiences incident pain on a background of stable pain control while taking regular opioids, give additional oral short-acting opioids at a dose equivalent to one-sixth of total 24-hour dose or buccal fentanyl preparations. (EAPC, NHS, SIGN)
P9. If the person experiences movement-related pain, give pre-emptive analgesia before activity that is likely to cause pain. (EAPC, NCCN, NHS, SIGN)
P10. For patients with neuropathic pain, consider the following options (EAPC, ESMO, NCCN, SIGN): • Anticonvulsant agents (gabapentin, pregabalin or carbamazepine) • Antidepressants (amitryptiline, nortryptiline or venlafaxine).
P11. For patients with bone pain due to cancer, consider bisphosphonates. (ESMO, NCCN, NHS, SIGN)
P12. For patients with painful bone metastases, consider single-fraction radiotherapy. (ESMO, NCCN, NHS, SIGN)
P13. Consider denosumab for bone pain from metastatic breast cancer. (Consensus) Evidence from a randomised clinical trial: Cleeland, C.S., et al., Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer, 2012. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22951813
P14. For patients with refractory pain despite carefully titrated doses of conventional medical therapies, consider whether a nerve block or intrathecal route of administration may be indicated. (NCCN, NHS, SIGN)
P15. Consider nerve blocks for well-localised pain syndromes (e.g. coeliac plexus block for pain in pancreas or upper abdomen). (NCCN)
P16. Consider intrathecal infusion of analgesic for patients with: • difficult-to-control pain. (EAPC) • diffuse pain. (NCCN) • unacceptable opioid-related toxicity despite optimal use of adjuvants and a trial of switching opioids. (SIGN)
P17. For patients with renal impairment, carefully monitor for treatment-related adverse effects. If opioid-related adverse effects occur, consider the following options:

Recommendation
• Reduce the total dose of regular opioid (either by reducing dose and maintaining dose interval, or increasing dose interval and maintaining dose). (ESMO, SIGN) • Switch to immediate-release opioid. (SIGN) • Switch to a different opioid (e.g. consider alfentanil, buprenorphine or fentanyl instead of morphine, codeine or hydromorphone). (EAPC, ESMO, NCCN, SIGN)
P18. Morphine should be used with caution in patients with severe kidney disease(GFR <30 mL/min/1.73 m2) in whom it may require reductions in dose and frequency. (EAPC, SIGN)
P19. If opioid toxicity is suspected (Consensus): The Working Group considered principles of holistic management and potential for drug–drug interactions • Review all medicines and consider whether medicines may be contributing to the signs and symptoms. • Take a detailed history and consider whether the person's underlying disease (e.g. brain metastases, hepatic impairment) or other factors may be contributing to the signs and symptoms. • Complete a thorough physical examination. • Consider further investigations.
P20. If opioid-related toxicity of the central nervous system is suspected, consider undertaking the following investigations (Consensus): • Ask about history of fever, dysuria, cough. • Check electrolytes (sodium, potassium, chloride), urea, creatinine. • Perform urine dipstick test. • Order chest X-ray.
P21. If opioid-related toxicity of the central nervous system is not ruled out after investigation (NHS): • Consider supplemental hydration if the patient is dehydrated. • Consider switching to a different opioid or reducing dose.
P22. If confusion or delirium is present, manage according to life expectancy (Consensus): • If NOT last days of life, trial non-pharmacological management first. If not adequately improved, consider an antipsychotic agent. • If last days of life and the person is at risk of self-harm or harm to others, consider antipsychotic agent.

Recommendation
P23. If myoclonus is present, manage according to life expectancy (Consensus): • If NOT last days of life, manage reversible causes and avoid benzodiazepines. • If last days of life, benzodiazepines may be considered.
P24. If opioid-related pruritis is suspected, exclude renal impairment and hepatic impairment as cause. (Consensus)
P25. Manage opioid-related pruritis with either or both the following: • Consider switching to a different opioid. (NCCN, NHS) If pruritis persists despite opioid switching after trialling more than one opioid, refer to palliative care team or palliative medicine expert for specialist review. (Consensus) • Consider symptomatic management with an H1 antihistamine (choose one of the newer, less sedating agents). (Consensus)
P26. If opioid-related respiratory depression is suspected (Consensus): • Eliminate other causes (e.g. excessive oxygen flow). • Check hydration status. • For patients receiving methadone, consult a clinical pharmacologist or palliative care physician. Respiratory depression is an uncommon adverse effect of opioid therapy for cancer pain
P27. Manage opioid-related respiratory depression with all of the following (Consensus): • Withhold opioid dose and recommence either at lower dosing frequency or reduced dose. • Ensure the person is positioned properly. • Rehydrate if dehydrated.
P28. If a patient is experiencing opioid-related mouth dryness: • Ensure adequate mouth care. (NHS) • Consider switching to another opioid. (Consensus)
P29. Reduce the risk of constipation in non-terminal patients using all of the following strategies: • Maintain adequate hydration. (NCCN) • Encourage physical activity (ambulant patients). (NCCN) • Provide education on bowel hygiene routine. (Consensus)

Recommendation
• Use a combination of stimulant and softening laxatives (EAPC, NCCN, NICE, SIGN) • Avoid other agents that can aggravate constipation (e.g. 5HT3 antagonists), if possible. (Consensus)
P30. For an ambulant non-terminal patient with critical constipation caused by opioids, which is not responding to oral stimulant and softening laxatives, consider one of the following options: • Switch opioid. (NICE) • Switch to a combination oxycodone hydrochloride with naloxone hydrochloride. (Consensus) The combination of oxycodone hydrochloride and naloxone hydrochloride has not been compared with laxatives in this patient population. (NPS Radar. Oxycodone-with-naloxone controlled-release tablets (Targin). 2011(December) [cited 2012 20th October]; Available from: http://www.nps.org.au/__data/assets/pdf_file/0005/135869/oxycodone_with_naloxone.pdf) • Manage symptoms with methylnaltrexone. (NCCN, EAPC)
P31. At each opioid dose increment, routinely prescribe a prophylactic antiemetic (e.g. prochlorperazine maleate , metoclopramide or haloperidol). (EAPC, NCCN, NICE)
P32. If nausea persists after symptom review, consider prescribing an antiemetic to be taken regularly. (ESMO, NCCN, NHS, NICE)
P33. If nausea is persistent or severe, investigate further to determine causes (e.g. constipation, central nervous system pathology, chemotherapy, radiation therapy). (NCCN)
P34. If opioid-induced hyperalgesia is suspected (e.g. pain is escalating despite pain management according to these guidelines), refer to palliative care team or palliative medicine specialist. (Consensus)
P35. Consider urinary retention in patients with urinary symptoms. (Consensus)
P36. Consider switching to a different opioid in either of the following situations: • Optimal pain relief cannot be achieved despite appropriate dose. (ESMO, NCCN, NHS, NICE) • The patient is experiencing unacceptable opioid-related adverse effects. (EAPC) • The route of administration is no longer possible. (NHS)
P37. If switching to a different formulation or route of administration with the same agent, use the equivalent total 24-hour opioid dose. (EAPC, ESMO, NCCN, NHS, NICE)
P38. If switching to a different agent because the previous route of administration is no longer possible, consider a starting dose lower than the equivalent total 24-hour opioid dose of the previous agent. (EAPC)
P39. If switching to a different opioid agent due to unacceptable treatment-related adverse effects,

Recommendation
despite optimal pain relief, start with a lower dose, then adjust dose carefully while monitoring for pain control and adverse effects. (EAPC, ESMO)
P40. If there is reason to suspect that a patient's prescribed opioids are being misused or diverted: • Explain the person that goal is pain relief without misuse. (Consensus) • Assess for opioid dependency disorder. (Consensus) • Establish a treatment agreement with the person, including an agreement to limit the supply of opioids to a single prescriber and pharmacy. (NCCN)
P41. Advise all patients and carers to ensure medicines are kept out of children's reach. (Consensus)
P42. For patients taking opioids, assess capacity to drive using current national guidelines (Austroads Limited. Assessing fitness to drive. Medical standards for licensing and clinical management guidelines. Sydney: Austroads Ltd; 2012. Available at http://www.austroads.com.au). (Consensus)
P43. If pain is not adequately controlled despite recommended pain management strategies, including analgesic medication, consult a pain specialist. (NICE, NHS)

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2.2.6 Non-pharmacological management

Recommendation
N1. Consider referral to a physiotherapist for assessment of functional ability and potential suitability of non-pharmacological pain management strategies. (NCCN, NHS, SIGN)
N2. Provide support for any psychosocial and spiritual concerns identified during comprehensive assessment. (NCCN)
N3. Consider referral to an occupational therapist for assessment and management. (NCCN, NHS)
N4. Consider referral to a clinical psychologist for psychological therapies and support: • Cognitive–behavioural therapy (NCCN, SIGN) • Relaxation techniques (NCCN) • Distraction techniques (NCCN) • Guided imagery therapy. (NCCN)

Recommendation
N5. Consider music either prerecorded or with a music therapist (Consensus) Systematic review by Bradt et al (2011): Bradt J, Dileo C, Grocke D, Magill L. Music interventions for improving psychological and physical outcomes in cancer patients.Cochrane Database Syst Rev. 2011 Aug 10;(8):CD006911. doi: 10.1002/14651858.CD006911.pub2.
N6. Offer to discuss any complementary therapies the person may wish to consider, and provide reliable information about the evidence for their effectiveness. (Consensus) Principles of holistic management; Potential for drug–drug interactions

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3 Flowchart overview

Overview

4 Patient-centred care

4.1 Patient-centred care

Evidence-based recommendation
PCC1. Routinely establish a multidisciplinary team approach to pain management that involves allied care health professionals and primary care health professionals according to the person's pain management needs and preferences. (SIGN)

Evidence-based recommendation

PCC2. Adopt a person-centred approach to pain management (NICE), which involves:

- taking into account the patient's needs and preferences
- enabling the person to make informed decisions about their care and treatment
- providing culturally appropriate care and information
- involving the person's partner, carer or family in treatment decisions, if the person wishes.

4.2 References

National Institute of Clinical Excellence Guideline Development Group. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. NICE clinical guideline 140. Manchester: NICE; 2012. Available from: http://www.nice.org.uk/nicemedia/live/13745/59285/59285.pdf

Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline [Version amended 18 July 2011] Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk/pdf/SIGN106.pdf

5 Screening

5.1 Screening

Evidence-based recommendation

S1. For all patients who are able to communicate their level of pain, assess worst, least and usual pain intensity during the previous 24 hours using a self-reported numerical rating scale from zero to 10, where zero represents 'no pain' and 10 represents 'worst pain you can imagine'. (NCCN)

Numerical rating scale for pain intensity

Verbal: What number describes your worst/least/average pain, where zero is no pain and ten is worst pain you can imagine.

Written: Please circle the number that best describes your worst/least/average pain over the past 24 hours:

Evidence-based recommendation

S2. For people who cannot self-report due to cognitive impairment, use the Abbey Pain Scale. (Consensus)

Recommended by the Australian Pain Society: Australian Pain Society. Residential Aged Care Facilities - Management Strategies. Sydney: Australian Pain Society; 2005. Available from: http://www.apsoc.org.au/owner/files/9e2c2n.pdf APS 2005.

Complete a comprehensive assessment if:

- pain score is 2 or more on self-reported numerical rating scale of zero to 10
- pain score is 3 or more on the Abbey Pain Scale
- the patient has experienced new pain or a sudden, unexpected change in intensity of pain.

5.2 References

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. Version 1.2012: NCCN; 2012. Available from: http://www.nccn.org

6 Assessment

6.1 Assessment

Evidence-based recommendation

A1. Routinely assess all the following to determine the individual's pain management needs:

• Disease status and treatment (Consensus)

The Working Group considered this information to provide necessary context for other assessments

• Pain severity (using a validated tool) (NCCN, SIGN)

Evidence-based recommendation

• Pain experience (location, interference, timing, description, aggravating and relieving factors) (ESMO, NCCN, NHS, SIGN)

• Current and previous management of pain (ESMO, NCCN, NHS, SIGN) and other symptoms (Consensus)

The Working Group considered principles of holistic management and potential for drug–drug interactions

• Pain meaning for the person and their beliefs and knowledge (NCCN, NHS, SIGN)

• Psychosocial status (ESMO, NCCN, NHS, SIGN)

• Concern about pain and its treatment (e.g. perceived addictiveness of opioids) (NICE)

• Cognitive functioning (Consensus)

The Working Group considered this information to provide necessary context for other assessments

• Physical examination and, where needed, further investigations (NCCN, NHS, SIGN)

• Functional status (ESMO)

• Risk factors for poorly controlled pain or opioid misuse (NCCN)

• Patient and family preferences (goals and expectations for comfort, advance directives) (NCCN)

• Factors suggesting an oncological emergency. (NCCN)

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6.2 Assessment checklist

6.2.1 [ ] Disease status and treatment

[ ] Record the person's disease status:

- Cancer type
- Site/s

[ ] Record current cancer treatments, including:

- Chemotherapy (agents, doses)
- Radiotherapy (site, dose)

[ ] Record previous and previous cancer treatments, including:

- Chemotherapy (agents, doses)
- Radiotherapy (site, dose)

Anticancer treatments that may cause peripheral neuropathy

Taxanes

Platinum agents

Eribulin

Vincristine

Navelbine

Lenolinamide

Bortezomib

Thalidomide

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6.2.2 [ ] Pain severity

[ ] Record pain severity in detail, using a self-reported validated pain assessment instrument (e.g. the Brief Pain Inventory short form (BPI-SF) recommended by NCCN and SIGN)

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6.2.3 [ ] Pain experience

If the person has more than one pain, number each and complete all assessments for each pain (including any pain not caused by cancer).

6.2.3.1 [ ] Location

[ ] Assess and record:

- Location (see the Change Pain website for an interactive and printable body diagram)
- Presence of radiating pain

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6.2.3.2 [ ] Interference with activities

[ ] Assess and record whether and how pain is interfering with the person's daily activities (e.g. walking , sleeping), using a validated assessment tool (e.g. the Brief Pain Inventory short-form (BPI-SF) recommended by NCCN and SIGN)

If pain is impairing the person's ability to perform activities of daily living, consider referral to a physiotherapist or occupational therapist for further assessment.

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6.2.3.3 [ ] Timing

[ ] Assess and record the timing of pain, including:

- Onset
- Duration
- Change in pain over time
- Pain during particular movements or activities
- Whether pain is persistent or intermittent
- Whether pain is generally controlled by medication but recurs at certain times or at end of dosing interval.

Aim to establish whether timing of pain is predictable or random and whether breakthrough analgesia might be needed preemptively.

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6.2.4 [ ] Description

[ ] Assess and record the quality of pain. Allow the patient to describe his/her pain, prompting with the descriptors listed below if needed.

Characteristic of nociceptive pain	**Characteristic of neuropathic pain**
Aching	Burning
Cramping	Electrical
Gnawing	Shock-like
Pressure	Shooting
Sharp	Tingling
Stabbing	
Throbbing	

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6.2.4.1 [ ] Aggravating and relieving factors

[ ] Assess and record factors that either make pain worse or relieve pain.

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6.2.4.2 [ ] Previous and current management of pain and other symptoms

[ ] Ask the patient which pain medications he or she:

- is currently taking
- has taken in the past.

[ ] Ask the patient which medications for other symptoms he or she:

- is currently taking
- has taken in the past.

[ ] For each medication, ask about:

- when it was taken (currently/ past month/before past month)
- duration of use
- dose
- efficacy
- adverse effects
- who prescribed it
- self-reported adherence
- reason for stopping (if applicable).

[ ] Ask the patient if he or she has used any non-pharmacological methods for managing pain (e.g. relaxation, massage, herbal medicine).

[ ] For each non-pharmacological pain management method, ask about:

- reason for use
- duration of use
- efficacy
- adverse effects
- reason for stopping (if applicable).

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6.2.4.3 [ ] Other symptoms

[ ] Assess and record the presence of other symptoms and attempt to diagnose the cause and mechanism of each.

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6.2.4.4 [ ] Pain meaning, beliefs and knowledge

[ ] Assess and record the meanings the person’s pain has for them and their family or carers.

[ ] Assess and record any concerns the person has about the pain and its treatment such as fear of addiction, tolerance, side effects and fear that prescription of opioid means the final phase of illness.

Provide education tailored to patients' and families' knowledge, beliefs and attitudes about pain and pain treatment.

Suggested questions to ask person:

What do you think is causing the pain?

Has someone else in the family had cancer pain?

Is there anything you are afraid of related to the pain or its management?

Is there anything that worries you about the treatment of pain?

Source: Kissane D, Bultz B, Butow P, Finlay I, editors. Handbook of communication in oncology and palliative care. Oxford: Oxford University Press; 2010.

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6.2.4.5 [ ] Psychosocial assessment

[ ] Assess and record psychosocial status, including anxiety and depression.

[ ] Record psychiatric history, including previous or current substance abuse.

[ ] Assess risk of opioid misuse.

[ ] Assess and record relevant spiritual, religious or existential beliefs affecting pain and its management.

Suggested questions to assess risk of opioid misuse:

At any time in your life, have you ever used alcohol, cannabis, other drugs, or any substance that can lead to dependence, including a medicine normally prescribed by a doctor?

[For each substance named]

Do you think your use of [substance] was out of control?

- Never or almost never
- Sometimes
- Often
- Always or nearly always

Did the prospect of missing a drink/fix/dose of [substance] make you anxious or worried?

- Never or almost never
- Sometimes
- Often
- Always or nearly always

Did you worry about your use of [substance]?

- Never or almost never
- Sometimes
- Often
- Always or nearly always

Did you wish you could stop?

- Never or almost never
- Sometimes
- Often
- Always or nearly always

How difficult did you find it to stop or to go without [substance]?

- Not difficult
- Quite difficult
- Very difficult
- Impossible

Has anyone in your immediate family (e.g. a parent, brother or sister) ever been addicted to or dependent on any substance, including alcohol, other substances (such as cannabis or other drugs), or a medicine normally prescribed by a doctor?

Adapted from: Gossop M, Darke S, Griffiths P, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995; 90: 607–14. Available from: www.ncbi.nlm.nih.gov/pubmed/7795497

Suggested questions to assess contribution of spiritual beliefs to pain and its management

Do you have spiritual beliefs that help you cope?

What importance does your faith or belief have in your life?

How does your faith or belief affect the way you think about your pain?

Where psychosocial concerns are identified, refer to the following guideline for advice on further assessment, referral and management - National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown, NSW: National Breast Cancer Centre; 2003. Available from: http://canceraustralia.gov.au/publications-resources/cancer-australia-publications/clinical-practice-guidelines-psychosocial-care

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6.2.4.6 [ ] Cognitive assessment

[ ] Record whether cognitive impairment is present.

If self-reporting of pain intensity is difficult due to cognitive impairment, use a tool validated for this population such as the Abbey Pain Scale

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6.2.4.7 Physical examination and further investigations

[ ] Perform a thorough physical examination

[ ] Consider whether there are indications for imaging or laboratory studies.

A sudden change in the type or intensity of pain warrants further investigations.

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6.2.4.8 [ ] Functional status

[ ] Assess and record functional status, using a systematic approach.

Consider using one of the following:

- The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale
- The Australia-modified Karnofsky Performance Status (AKPS) scale

If pain is contributing to functional impairment, consider referral to physiotherapist, occupational therapist, social worker or palliative care team.

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6.2.4.9 [ ] Risk factors for poorly controlled pain

[ ] Assess and record whether the person has any risk factors for poor pain control:

- high pain score
- cognitive impairment
- elderly
- history of substance use
- first language other than English
- membership of a cultural minority group
- neuropathic pain.

If self-reporting of pain intensity is difficult due to cognitive impairment, use the Abbey Pain Scale

For patients whose ability to communicate with the treating team may be affected by a language barrier, use a healthcare interpreter.

The Brief Pain Inventory is available in many community languages (listed on the MD Anderson Cancer Center website).

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6.2.4.10 [ ] Preferences for care based on individual's goals and expectations for comfort

[ ] Assess and record person's goals for comfort.

Suggested questions to ask person

What are you hoping to do with improved pain relief which you can't do now? (e.g. sleep better, be more active)

What aspects of daily life are you most hoping pain management can help with?

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6.2.4.11 [ ] Oncological emergencies

[ ] Consider whether pain is related to an oncological emergency, e.g:

- bone fracture (or high risk of imminent fracture)
- brain metastasis
- epidural metastasis
- leptomeningeal metastasis
- infection
- obstructed or perforated abdominal organ.

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6.3 References

Gossop M, Darke S, Griffiths P, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995; 90: 607–14.

Kissane D, Bultz B, Butow P, Finlay I, editors. Handbook of communication in oncology and palliative care. Oxford: Oxford University Press; 2010.

National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown, NSW: National Breast Cancer Centre; 2003. Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp90.pdf

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. Version 1.2012: NCCN; 2012. Available from: http://www.nccn.org

National Health Service Quality Improvement Scotland. Best practice statement. The management of pain in patients with cancer. Edinburgh: NHS Quality Improvement Scotland; 2009. Available from: http://www.palliativecareguidelines.scot.nhs.uk/documents/PAINCANCERREV_BPS_NOV09.pdf

National Institute of Clinical Excellence Guideline Development Group. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. NICE clinical guideline 140. Manchester: NICE; 2012. Available from: http://www.nice.org.uk/nicemedia/live/13745/59285/59285.pdf

Ripamonti CI, Bandieri E, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol 2011; 22(Suppl 6): vi69-vi67. Available from: http://annonc.oxfordjournals.org/content/22/suppl_6/vi69.long

Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline [Version amended 18 July 2011] Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk/pdf/SIGN106.pdf
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6.4 Appendices

6.4.1 Appendix: The Eastern Cooperative Oncology Group (ECOG) Performance Status scale

Grade	Person's function
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group (Chair: Robert Comis) Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655. Available from: http://www.ecog.org/general/perf_stat.html.

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6.4.2 Appendix: The Australia-modified Karnofsky Performance Status (AKPS) scale

Score (Category)	Person's function
100 (A)	Normal; no complaints; no evidence of disease
90 (A)	Able to carry on normal activity; minor signs or symptoms
80 (A)	Normal activity with effort; some signs or symptoms of disease
70 (B)	Cares for self; unable to carry on normal activity or to do active work
60 (B)	Requires occasional assistance but is able to care for most of his needs
50 (B)	Requires considerable assistance and frequent medical care
40 (C)	In bed more than 50% of the time
30 (C)	Almost completely bedfast
20 (C)	Totally bedfast and requiring extensive nursing care by professionals and/or family
10 (C)	Comatose or barely arousable
0	Dead

Source: Abernethy AP, Shelby-James T, Fazekas BS, et al. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice SRCTN81117481]. BMC Palliat Care 2005; 4: 7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1308820/?tool=pubmed.

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7 Self-management

7.1 Patient-awareness and self-management

Evidence-based recommendation
E1. For all patients, provide education about cancer-related pain and its management. (NCCN, SIGN)

Evidence-based recommendation
E2. Consider including information about all of the following:

Evidence-based recommendation

• pain causes

• common experiences of cancer pain (e.g. onset, timing)

• effective treatments (including medicines and non-pharmacological management strategies)

• common attitudes and beliefs that may prevent people with cancer receiving effective pain control (e.g. fears that opioids are addictive and used only at the end of life, and that patients will develop tolerance over time requiring dose escalation)

• side-effects of medicines

• any safety concerns (e.g. mixing with alcohol, driving)

• how to work with health professionals to achieve the best pain control possible (e.g. the importance of reporting rather than concealing pain, side-effects and other concerns about medication)

• ways to ensure patients have adequate access and supply to prescribed opioids. (Consensus)

Systematic review by Koller et al (2012): Koller A, Miaskowski C, De Geest S, Opitz O, Spichiger E. A systematic evaluation of content, structure, and efficacy of interventions to improve patients' self-management of cancer pain. J Pain Symptom Manage. 2012 Aug;44(2):264-84.

Evidence-based recommendation

E3. Include the person’s family and carers in education about pain and its management, if appropriate. (Consensus)

Carers are frequently involved in decision-making (e.g. to start and adhere to opioids) and management

Educational resources for patients, families and health professionals

Overcoming cancer pain – booklet and DVD (Cancer Council NSW)

Includes information, resources (e.g. helplines), a pain measurement scale and a prompt list of questions to ask medical staff.

Use of this resource has been shown to reduce pain by a randomised controlled trial (Lovell MR, Forder P, Stockler M, Butow PN, Briganti E, Chye R, et al. A randomised controlled trial of a standardised educational intervention for patients with cancer pain. Journal of Pain and Symptom Management. 2010; 40:49-59. [Available at: www.ncbi.nlm.nih.gov/pubmed/20619212])

Copies are available via Cancer Council NSW website.

CareSearch

CareSearch, the Australian palliative care knowledge network, offers a number of resources both for patients and health professionals.

Managing pain with strong opioids in people with advanced, progressive disease (NICE)

A booklet for people using opioid treatment is available from the UK National Institute of Clinical Excellence (NICE) as part of their guideline on opioids via http://guidance.nice.org.uk/CG140/PublicInfo/doc/English

NICE also provide a training resource for health professionals on opioid prescribing in palliative care via: http://guidance.nice.org.uk/CG140/EducationResource/doc/English

Notice: A version of this Australian guideline for patients and their families and carers and educational resources for health professionals will become available on this page in 2013.

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7.1.1 References

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. Version 1.2012: NCCN; 2012. Available from: http://www.nccn.org

Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline [Version amended 18 July 2011] Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk/pdf/SIGN106.pdf

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8 Pharmacological Management

Contents

8.1 Pharmacological management

Please refer to Approved Product information before prescribing any agent discussed in this guideline

Exclude causes other than cancer before commencing opioid therapy for pain - see comprehensive assessment

Dose reduction may be needed for elderly patients

Use the eviQ tool for calculating dose equivalents for opioid preparations available in Australia

8.1.1 Regular analgesia

Evidence-based recommendation
P1. For patients with continuing pain, begin regular analgesia with paracetamol or a nonsteroidal anti-inflammatory drug (NSAID). (ESMO, NCCN, SIGN)

Evidence-based recommendation
P2. If pain continues despite treatment with paracetamol or NSAIDs, consider regular oral opioids. For patients with normal renal and hepatic function, start with a low dose (e.g. morphine 20–30 mg per day (10–15 mg bd or 5 mg q4h) with 5 mg rescue doses as needed for breakthrough pain. (EAPC,ESMO,NCCN)

Evidence-based recommendation

P3. If pain continues or recurs despite regular oral opioid analgesia and the patient feels that analgesia is inadequate, consider either of the following options:

• Add a NSAID (if the person is not already taking and NSAID and has no contraindications). (EAPC) Read note

Weak evidence that the addition of NSAID to WHO Step III opoiods can improve analgesia or reduce opioid does requirement

• Increase the regular dose to incorporate the rescue doses (SIGN), then reassess pain severity and adverse effects within 48 hours. (Consensus)

Sample calculation

A patient taking 5 mg morphine q4h requires three extra 5 mg rescue doses for breakthrough pain. The resulting total 24-hour dose is 45 mg morphine. The new regular analgesic regimen is morphine 7.5 mg q4h, with a new rescue dose of 7.5 mg.

Evidence-based recommendation

P4. Methadone should be prescribed and titrated with guidance from specialists familiar with its use. (EAPC, ESMO, NCCN)

Evidence-based recommendation

P5. The transdermal route of administration can be considered as an alternative to oral administration if required, for reduced risk of constipation or patient convenience. (EAPC) Use one of the following options:

• Switch to transdermal fentanyl. Note: A 12 mcg fentanyl transdermal patch is equivalent to 45 mg morphine daily. (NICE)

• Switch to transdermal buprenorphine (suitable for patients with stable mild pain only). Note: A 20 mcg buprenorphine transdermal patch is equivalent to 30 mg morphine daily. (NICE)

Due to long duration of action, the transdermal route should be considered only when pain is stable. (ESMO, NCCN, SIGN)

Before prescribing opioids, check renal function and titrate dose accordingly. More information about pain management in patients with renal impairment

NSAIDs are associated with gastrointestinal, cardiovascular and renal adverse effects and should be used with caution, particular in patients aged over 65 years. Gastrointestinal risk is increased in patients with a past history of upper gastrointestinal tract bleeding , NSAID-related ulcer or Helicobacter pylori infection. Cardiovascular risk is increased in patients with other cardiovascular risk factors. Risk of renal impairment is increased in patients with pre-existing renal impairment, chronic heart failure or cirrhosis and in those taking diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, aspirin or other nephrotoxic drugs, and in patients on a salt-reduced diet [Therapeutic Guidelines version revised June 2009 (etg37 July 2012)].

Provide information and education for patients and carers about cancer pain management, including the benefits and risks of opioid medicines. (Patients and health professionals commonly have concerns about addiction, tolerance and dependence that are disproportionate to the risks.) See also Education section.

If the prescribing clinician or other staff are unfamiliar with an analgesic agent under consideration, consult a pain specialist and a clinical pharmacologist who are familiar with the use of the agent.

One month’s supply is available on PBS Authority with approval by telephone for the following opioids for cancer pain: combination codeine 30 mg/paracetamol 500 mg, oxycodone, morphine, hydromorphone.

For patients with a specific pain syndrome, consider an adjuvant.

Preventing, monitoring and managing adverse effects of opioids

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8.1.2 Additional prescribed analgesic for breakthrough pain

Evidence-based recommendation
P6. In addition to regular opioids, routinely prescribe short-acting analgesia at a dose equivalent to one-sixth

Evidence-based recommendation
of total 24-hour dose, to be administered if breakthrough pain occurs. (NHS, SIGN)

Evidence-based recommendation
P7. If breakthrough pain occurs, re-titrate the regular opioid 24-hour dose. (SIGN)

Evidence-based recommendation
P8. If the person experiences incident pain on a background of stable pain control while taking regular opioids, give additional oral short-acting opioids at a dose equivalent to one-sixth of total 24-hour dose or buccal fentanyl preparations. (NHS, SIGN, EAPC)

Evidence-based recommendation
P9. If the person experiences movement-related pain, give pre-emptive analgesia before activity that is likely to cause pain. (EAPC, NCCN, NHS, SIGN)

Nerve blocks can be considered for refractory incident pain.

Transmucosal fentanyl (i.e. lozenges) is not recommended as first-line treatment for breakthrough pain.

More information about re-titrating the opioid dose for breakthrough pain under #Regular analgesia.

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8.1.3 Adjuvants

Evidence-based recommendation
P10. For patients with neuropathic pain, consider the following options (EAPC, ESMO, NCCN, SIGN):

Evidence-based recommendation
• Anticonvulsant agents (gabapentin, pregabalin or carbamazepine) • Antidepressants (amitryptiline, nortryptiline or venlafaxine).

Anticonvulsants may interfere with chemotherapy.

For anticonvulsants, start at a low dose and titrate according to benefit and adverse effects.

Gabapentin is not reimbursed by PBS for use in pain management. Carbamazepine is not registered for the management of neuropathic pain due to cancer.

If the prescribing clinician or other staff are unfamiliar with an adjuvant agent under consideration, consult a pain specialist and a clinical pharmacologist who are familiar with the use of the agent.

Evidence-based recommendation
P11. For patients with bone pain due to cancer, consider bisphosphonates. (ESMO, NCCN, NHS, SIGN)

Bisphosphonates should be prescribed with caution in patients with renal impairment.

Bisphosphonates have been associated with osteonecrosis of the jaw. The risk is increased after dental extractions and by periodontal disease. The Therapeutic Goods Administration (Australian Government Department of Health and Ageing) encourages health professionals prescribing bisphosphonates to:

• consider dental referral of the patient before starting treatment, especially for people at increased risk, such as the elderly

• reinforce the importance of good oral hygiene

• inform patients of the symptoms of osteonecrosis of the jaw that may occur while taking or after being given a bisphosphonates, such as "toothache" or pain, swelling or numbness of an area of the jaw or a discharge around a dental implant

• advise their patients that they should notify their dentist that they are taking or have been given a bisphosphonates. [See http://www.tga.gov.au/safety/alerts-medicine-bisphosphonate-071211.htm]

Bisphosphonate	TGA-approved Australian indications include:
Disodium pamidronate	Treatment of tumour-induced hypercalcaemia Treatment of predominantly lytic bone metastases from breast cancer, advanced mu myeloma
Ibandronate sodium	Treatment of metastatic bone disease in patients with breast cancer (tablets, injectio Treatment of tumour-induced hypercalcaemia, with or without metastases (injection)
Sodium clodronate	Treatment of hypercalcaemia of malignancy Treatment of osteolytic lesions (breast cancer metastases, multiple myeloma)
Zoledronic acid	Treatment of tumour-induced hypercalcaemia Prevention of skeletal related events in advanced malignancy involving bone

TGA: Therapeutic Goods Administration

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8.1.4 Anti-cancer treatment

Evidence-based recommendation
P12. For patients with painful bone metastases, consider single-fraction radiotherapy. (ESMO, NCCN, NHS,

Evidence-based recommendation
SIGN)

Evidence-based recommendation
P13. Consider denosumab for bone pain from metastatic breast cancer. (Consensus) Evidence from a randomised clinical trial: Cleeland, C.S., et al., Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer, 2012. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22951813

Denosumab is associated with increased risk of hypocalcaemia. The starting dose should be low and reassessed after 1 week.

Denosumab is associated with osteonecrosis of the jaw. Dental review is recommended before and after starting denosumab treatment.

Denosumab (RANK ligand monoclonal antibody) is registered in Australia for the treatment of skeletal-related events in patients with bone metastases from solid tumours. It is listed on the PBS for the treatment of bone metastases in patients with breast cancer or castration resistant prostate cancer.

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8.1.5 Interventional therapy

Evidence-based recommendation
P14. For patients with refractory pain despite carefully titrated doses of conventional medical therapies, consider whether a nerve block or intrathecal route of administration may be indicated. (NCCN, NHS, SIGN)

Evidence-based recommendation
P15. Consider nerve blocks for well-localised pain syndromes (e.g. coeliac plexus block for pain in pancreas or upper abdomen). (NCCN)

Evidence-based recommendation
P16. Consider intrathecal infusion of analgesic for patients with: • difficult-to-control pain. (EAPC) • diffuse pain. (NCCN) • unacceptable opioid-related toxicity despite optimal use of adjuvants and a trial of switching opioids. (SIGN)

More information about opioid switching.

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8.1.6 Preventing, monitoring and managing adverse effects of opioids

8.1.6.1 Routine prevention of adverse effects and education

Ensure adequate mouth care for all patients receiving opioids.

Explain to patients starting opioids that constipation is a very common side effect, and provide education about preventive bowel care.

Provide patients with information about the prevalence of opioid-related emesis and education about non-pharmacological management (e.g. avoiding strong smells).

Explain to all patients starting opioid treatment that experiencing nightmares is a common side-effect.

More information about patient education

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8.1.6.2 Renal impairment

Evidence-based recommendation
P17. For patients with renal impairment, carefully monitor for treatment-related adverse effects. If opioid-related adverse effects occur, consider the following options: • Reduce the total dose of regular opioid (either by reducing dose and maintaining dose interval, or increasing dose interval and maintaining dose). (ESMO, SIGN) • Switch to immediate-release opioid. (SIGN) • Switch to a different opioid (e.g. consider alfentanil, buprenorphine or fentanyl instead of morphine, codeine or hydromorphone). (EAPC, ESMO, NCCN, SIGN)

Evidence-based recommendation
P18. Morphine should be used with caution in patients with severe kidney disease(GFR <30 mL/min/1.73 m2) in whom it may require reductions in dose and frequency. (EAPC, SIGN)

Fentanyl can be used in patients with severe renal impairment, including patients on dialysis.

Methadone may be suitable for patients undergoing renal dialysis because it is not removed from the blood by dialysis.

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8.1.6.3 Assessment and management of opioid toxicity

Evidence-based recommendation

P19. If opioid toxicity is suspected (Consensus):

The Working Group considered principles of holistic management and potential for drug–drug interactions

• Review all medicines and consider whether medicines may be contributing to the signs and symptoms.

• Take a detailed history and consider whether the person's underlying disease (e.g. brain metastases, hepatic impairment) or other factors may be contributing to the signs and symptoms.

• Complete a thorough physical examination.

• Consider further investigations.

Signs and symptoms of severe opioid toxicity

Sedation

Respiratory depression

Myoclonus

Pinpoint pupils

Seizures

Opioid-related toxicity of the central nervous system

Cognitive impairment

Confusion

Delirium

Hallucinations

Myoclonus

Sedation

Evidence-based recommendation

P20. When opioid-related toxicity of the central nervous system is suspected, it is important to consider the differential diagnosis of causes of confusion/delirium, and consider undertaking the following investigations (Consensus):

• Ask about history of fever, dysuria, cough.

• Check electrolytes (sodium, potassium, chloride), urea, creatinine.

• Perform urine dipstick test.

• Order chest X-ray.

Evidence-based recommendation

P21. If opioid-related toxicity of the central nervous system is a probable cause (NHS):

• Consider supplemental hydration if the patient is dehydrated.

• Consider switching to a different opioid or reducing dose.

Evidence-based recommendation

P22. If opioid-related confusion or delirium is present, manage according to life expectancy. This includes managing the underlying aetiology (Consensus):

• If NOT last days of life, trial non-pharmacological management first to manage delirium symptoms. If the symptoms are not adequately improved, consider an antipsychotic agent.

• If last days of life and the person is at risk of self-harm or harm to others and/or is experiencing significant distress from the symptoms, consider an antipsychotic agent.

Evidence-based recommendation

P23. If opioid-related myoclonus is present, manage according to life expectancy (Consensus):

• If NOT last days of life, manage reversible causes and avoid benzodiazepines.

• If last days of life, benzodiazepines may be considered.

Evidence-based recommendation

P24. If opioid-related pruritis is suspected, exclude renal impairment and hepatic impairment as cause. (Consensus)

Evidence-based recommendation

P25. Manage opioid-related pruritis with either or both the following:

• Consider switching to a different opioid. (NCCN, NHS) If pruritis persists despite opioid switching after trialling more than one opioid, refer to a relevant specialist team (e.g. palliative care and/or pain medicine). (Consensus)

• Consider symptomatic management with an H1 antihistamine (choose one of the newer, less sedating agents). (Consensus)

Evidence-based recommendation

P26. If opioid-related respiratory depression is suspected (Consensus):

• Eliminate other causes (e.g. excessive oxygen flow).

• Check hydration status.

• For patients receiving methadone, consult a clinical pharmacologist or palliative care physician.

Respiratory depression is an uncommon adverse effect of opioid therapy for cancer pain

Evidence-based recommendation

P27. Manage opioid-related respiratory depression with all of the following (Consensus):

• Withhold opioid dose and recommence either at lower dosing frequency or reduced dose.

• Ensure the person is positioned properly.

• Rehydrate if dehydrated.

In patients receiving methadone it may be difficult to investigate the cause of respiratory depression for because of the variable half-life of methadone (1–120 hours).

Evidence-based recommendation

P28. If a patient is experiencing opioid-related mouth dryness:

• Ensure adequate mouth care. (NHS)

• Consider switching to another opioid. (Consensus)

Evidence-based recommendation

P29. Reduce the risk of constipation in non-terminal patients using all of the following strategies:

• Maintain adequate hydration. (NCCN)

• Encourage physical activity (ambulant patients). (NCCN)

• Provide education on bowel hygiene routine. (Consensus)

• Use a combination of stimulant and softening laxatives (EAPC, NCCN, NICE, SIGN)

• Avoid other agents that can aggravate constipation (e.g. 5HT3 antagonists), if possible. (Consensus)

Evidence-based recommendation

P30. For an ambulant non-terminal patient with critical constipation caused by opioids, which is not responding to oral stimulant and softening laxatives, consider one of the following options:

• Switch opioid. (NICE)

• Switch to a combination oxycodone hydrochloride with naloxone hydrochloride. (Consensus)

The combination of oxycodone hydrochloride and naloxone hydrochloride has not been compared with laxatives in this patient population. (NPS Radar. Oxycodone-with-naloxone controlled-release tablets (Targin). 2011(December) [cited 2012 20th October]; Available from: http://www.nps.org.au/__data/assets/pdf_file/0005/135869/oxycodone_with_naloxone.pdf)

• Manage symptoms with methylnaltrexone. (NCCN, EAPC)

For more information on management of constipation and bowel obstruction, refer to recommendations and guidance of the Palliative Care Clinical Studies Collaborative.

Evidence-based recommendation

P31. At each opioid dose increment, routinely prescribe a prophylactic antiemetic (e.g. prochlorperazine maleate , metoclopramide or haloperidol). (EAPC, NCCN, NICE)

Evidence-based recommendation

P32. If nausea persists after symptom review, consider prescribing an antiemetic to be taken regularly. (ESMO, NCCN, NHS, NICE)

Evidence-based recommendation

P33. If nausea is persistent or severe, investigate further to determine causes (e.g. constipation, central nervous system pathology, chemotherapy, radiation therapy). (NCCN)

Recommended first-line anti-emetic agents	
Haloperidol	0.5–1 mg orally every 6–8 hours
Metoclopramide hydrochloride	10–20 mg orally every hour as needed
Prochlorperazine	10 mg orally every 6 hours as needed

Source: NCCN

For more information on management of emesis, refer to recommendations and guidance of the Palliative C Studies Collaborative

Evidence-based recommendation

P34. If opioid-induced hyperalgesia is suspected (e.g. pain is escalating despite pain management according to these guidelines), refer to palliative care team or palliative medicine specialist. (Consensus)

Evidence-based recommendation

P35. Consider urinary retention in patients with urinary symptoms. (Consensus)

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8.1.6.4 Opioid rotation

Evidence-based recommendation

P36. Consider switching to a different opioid in either of the following situations:

• Optimal pain relief cannot be achieved despite appropriate dose. (ESMO, NCCN, NHS, NICE)

• The patient is experiencing unacceptable opioid-related adverse effects. (EAPC)

• The route of administration is no longer possible. (NHS)

Evidence-based recommendation

P37. If switching to a different formulation or route of administration with the same agent, use the equivalent total 24-hour opioid dose. (EAPC, ESMO, NCCN, NHS, NICE)

Evidence-based recommendation

P38. If switching to a different agent because the previous route of administration is no longer possible, consider a starting dose lower than the equivalent total 24-hour opioid dose of the previous agent. (EAPC)

Evidence-based recommendation

P39. If switching to a different opioid agent due to unacceptable treatment-related adverse effects, despite optimal pain relief, start with a lower dose, then adjust dose carefully while monitoring for pain control and adverse effects. (EAPC, ESMO)

Use the eviQ tool for calculating dose equivalence of transdermal fentanyl

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8.1.6.5 Preventing misuse of opioids

Evidence-based recommendation

P40. If there is reason to suspect that a patient's prescribed opioids are being misused or diverted:

• Explain the person that goal is pain relief without misuse. (Consensus)

• Assess for opioid dependency disorder. (Consensus)

• Establish a treatment agreement with the person, including an agreement to limit the supply of opioids to a single prescriber and pharmacy. (NCCN)

Evidence-based recommendation

P41. Advise all patients and carers to ensure medicines are kept out of children's reach. (Consensus)

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8.1.6.6 Assessing capacity to drive a vehicle

Evidence-based recommendation

P42. For patients taking opioids, assess capacity to drive using current national guidelines. (Consensus)

Austroads Limited. Assessing fitness to drive. Medical standards for licensing and clinical management guidelines. Sydney: Austroads Ltd; 2012. Available from: http://www.austroads.com.au

Cognitive performance is reduced early in treatment with opioids (mainly due to sedation) but the brain readily adapts. Therefore, a stable dose of opioid may not affect driving performance, provided the person is not taking other medicines that impair driving. (Austroads)

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8.1.7 Review and referral

Evidence-based recommendation
P43. If pain is not adequately controlled despite recommended pain management strategies, including analgesic medication, consult a pain specialist. (NICE, NHS)

If the prescribing clinician or other staff are unfamiliar with any agent under consideration, consult a pain specialist and a clinical pharmacologist who are familiar with the use of the agent.

Refer to the palliative care team or palliative medicine expert for specialist review if:

- opioid-related adverse effects persist despite opioid switching after trialling more than one opioid
- opioid-induced hyperalgesia is suspected.

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8.2 References

Austroads Limited, Assessing fitness to drive. Medical standards for licensing and clinical management guidelines. 2012, Austroads Ltd: Sydney. Available from: http://www.austroads.com.au

Caraceni A, Hanks G, Kaasa S, European Palliative Care Research Collaborative. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations for the EAPC. Lancet Oncol 2012; 13: e58-e68. Web version available from: http://www.eapcnet.eu/LinkClick.aspx?fileticket=i-bB4cvZyzg%3d&tabid=1794

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. Version 1.2012: NCCN; 2012. Available from: http://www.nccn.org

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Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer. A national clinical guideline [Version amended 18 July 2011] Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk/pdf/SIGN106.pdf

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9 Non-pharmacological Management

9.1 Non-pharmacological management

Evidence-based recommendation
N1. Consider referral to a physiotherapist for assessment of functional ability and potential suitability of non-pharmacological pain management strategies. (NCCN, NHS, SIGN)

Consider complementary therapies (see table below)

Evidence-based recommendation
N2. Provide support for any psychosocial and spiritual concerns identified during comprehensive assessment. (NCCN)

Evidence-based recommendation
N3. Consider referral to an occupational therapist for assessment and management. (NCCN, NHS)

Occupational therapists can assess activities of daily living, energy conservation, anxiety management, relaxation and lifestyle impact management, and assess potential benefits of diversional therapy, splints, role support, advice on functional ability, positional and seating assessment and advice, wheelchair, and assistive equipment.

Evidence-based recommendation

N4. Consider referral to a clinical psychologist for psychological therapies and support:

- Cognitive–behavioural therapy (NCCN, SIGN)
- Relaxation techniques (NCCN)
- Distraction techniques (NCCN)
- Guided imagery therapy. (NCCN)

Evidence-based recommendation

N5. Offer to discuss any complementary therapies the person may wish to consider, and provide reliable information about the evidence for their effectiveness. (Consensus)

Principles of holistic management; Potential for drug–drug interactions

Complementary therapies for cancer pain management

Modalities recommended in international guidelines	
Modality	**Source(s)**
Bed/bath/walking aids	NCCN
Cognitive–behavioural therapy	SIGN, NCCN
Distraction therapy	NCCN
Heat/ice therapy	NCCN
Imagery/hypnotherapy	SIGN, NCCN
Massage	NCCN, SIGN
Transcutaneous electrical nerve stimulation	

Modalities recommended in international guidelines	
Modality	**Source(s)**
(TENS)	NCCN
Reflexology	SIGN
Reiki	SIGN
Relaxation	NCCN
Therapeutic exercise	NHS

9.2 References

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National Health Service Quality Improvement Scotland. Best practice statement. The management of pain in patients with cancer. Edinburgh: NHS Quality Improvement Scotland; 2009. Available from: http://www.palliativecareguidelines.scot.nhs.uk/documents/PAINCANCERREV_BPS_NOV09.pdf

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10 Practice improvement

Practice improvement and quality control

Notice: Recommendations and resources for audit will be added to the next draft of this guideline

Relevant Australian initiatives include:

Palliatiative Care Australia National Standards Assessment Program

Palliative Care Outcomes Collaboration

11 Resources

Contents

11.1 Resources

11.1.1 International guidelines for cancer pain management

Caraceni A, Hanks G, Kaasa S, European Palliative Care Research Collaborative. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations for the EAPC. Lancet Oncol 2012; 13: e58-e68. Available from: http://www.eapcnet.eu/LinkClick.aspx?fileticket=i-bB4cvZyzg%3d&tabid=1794.

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11.1.2 Other relevant guidelines

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Palliative Care Expert Group. Therapeutic guidelines: palliative care. Version 3. Melbourne: Therapeutic Guidelines Limited; 2010. Available at: http://www.tg.org.au/index.php?sectionid=47

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11.1.3 Education

Caresearch (the Australian palliative care knowledge network)

Cancer Council Australia

UK National Institute of Clinical Excellence

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11.1.4 Prescribing information

NPS (formerly National Prescribing Service)

eviQ (Cancer treatments online: a service of Cancer Institute NSW)

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11.1.5 Other resources

Austroads guidelines for assessing fitness to drive

Australian Pain Society recommendations on pain assessment in people with cognitive impairment

eviQ tool for calculating dose equivalence

Palliatiative Care Australia National Standards Assessment Program

Palliative Care Outcomes Collaboration

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12 Opioid formulations

Opioid formulations

Information taken from the PBS A-Z Medicine Listing on 5th November 2012

Agent	Formulations and strengths
Morphine hydrochloride	Oral solution 2 mg per mL, 200 mL Oral solution 5 mg per mL, 200 mL Oral solution 10 mg per mL, 200 mL
Morphine sulfate	Tablet 10 mg Tablet 20 mg Tablet 30 mg Tablet 5 mg (controlled release) Tablet 10 mg (controlled release) Tablet 15 mg (controlled release) Tablet 30 mg (controlled release) Tablet 60 mg (controlled release) Tablet 100 mg (controlled release) Tablet 200 mg (controlled release) Capsule 30 mg (controlled release) Capsule 60 mg (controlled release) Capsule 90 mg (controlled release) Capsule 120 mg (controlled release) Capsule 10 mg (containing sustained release pellets) Capsule 20 mg (containing sustained release pellets) Capsule 50 mg (containing sustained release pellets)

Agent	Formulations and strengths
	Capsule 100 mg (containing sustained release pellets) Sachet containing controlled release granules for oral suspension, 20 mg per sachet Sachet containing controlled release granules for oral suspension, 30 mg per sachet Sachet containing controlled release granules for oral suspension, 60 mg per sachet Sachet containing controlled release granules for oral suspension, 100 mg per sachet Sachet containing controlled release granules for oral suspension, 200 mg per sachet Injection 10 mg in 1 mL Injection 15 mg in 1 mL Injection 30 mg in 1 mL
Morphine tartrate	Injection 120 mg in 1.5 mL
Buprenorphine	Tablet (sublingual) 400 micrograms (as hydrochloride) Tablet (sublingual) 2 mg (as hydrochloride) Tablet (sublingual) 8 mg (as hydrochloride) Transdermal patch 5 mg (releasing approximately 5 micrograms per hour) Transdermal patch 10 mg (releasing approximately 10 micrograms per hour) Transdermal patch 20 mg (releasing approximately 20 micrograms per hour)
	Lozenge 200 micrograms (as citrate) Lozenge 400 micrograms (as citrate) Lozenge 600 micrograms (as citrate) Lozenge 800 micrograms (as citrate) Lozenge 1200 micrograms (as citrate) Lozenge 1600 micrograms (as citrate)

Agent	Formulations and strengths
Fentanyl	Transdermal patch 2.063 mg (releasing approximately 12 micrograms per hour) Transdermal patch 2.1 mg (releasing approximately 12 micrograms per hour) Transdermal patch 2.55 mg (releasing approximately 25 micrograms per hour) Transdermal patch 4.125 mg (releasing approximately 25 micrograms per hour) Transdermal patch 4.2 mg (releasing approximately 25 micrograms per hour) Transdermal patch 5.10 mg (releasing approximately 50 micrograms per hour) Transdermal patch 8.25 mg (releasing approximately 50 micrograms per hour) Transdermal patch 8.4 mg (releasing approximately 50 micrograms per hour) Transdermal patch 1.28 mg (releasing approximately 12 micrograms per hour) Transdermal patch 7.65 mg (releasing approximately 75 micrograms per hour) Transdermal patch 12.375 mg (releasing approximately 75 micrograms per hour) Transdermal patch 12.6 mg (releasing approximately 75 micrograms per hour) Transdermal patch 10.20 mg (releasing approximately 100 micrograms per hour) Transdermal patch 16.5 mg (releasing approximately 100 micrograms per hour) Transdermal patch 16.8 mg (releasing approximately 100 micrograms per hour)
	Tablet 2 mg Tablet 4 mg

Agent	Formulations and strengths
Hydromorphone hydrochloride	Tablet 8 mg Tablet 4 mg (modified release) Tablet 8 mg (modified release) Tablet 16 mg (modified release) Tablet 32 mg (modified release) Tablet 64 mg (modified release) Oral liquid 1 mg per mL, 473 mL Injection 2 mg in 1 mL Injection 10 mg in 1 mL Injection 50 mg in 5 Ml Injection 500 mg in 50 mL
Methadone hydrochloride	Tablet 10 mg Oral liquid 25 mg per 5 mL, 200 mL Oral liquid 25 mg per 5 mL, 1 L Injection 10 mg in 1 mL
Oxycodone	Suppository 30 mg
Oxycodone hydrochloride	Tablet 5 mg Tablet 5 mg (controlled release) Tablet 10 mg (controlled release) Tablet 15 mg (controlled release) Tablet 20 mg (controlled release) Tablet 30 mg (controlled release) Tablet 40 mg (controlled release) Tablet 80 mg (controlled release) Capsule 5 mg Capsule 10 mg Capsule 20 mg

Agent	Formulations and strengths
	Oral solution 5 mg per 5 mL, 250 mL
Oxycodone hydrochloride with naloxone hydrochloride	Tablet 5 mg-2.5 mg (controlled release) Tablet 10 mg-5 mg (controlled release) Tablet 20 mg-10 mg (controlled release) Tablet 40 mg-20 mg (controlled release)
Tramadol hydrochloride	Tablet 100 mg (once a day extended release) Tablet 200 mg (once a day extended release) Tablet 300 mg (once a day extended release) Tablet 50 mg (twice daily sustained release) Tablet 100 mg (twice daily sustained release) Tablet 150 mg (twice daily sustained release) Tablet 200 mg (twice daily sustained release) Capsule 50 mg Oral drops 100 mg per mL, 10 mL Injection 100 mg in 2 mL

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