Appendix C Guideline scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults

1.1 Short title

Opioids for pain in palliative care

2 The remit

The Department of Health has asked NICE to produce a short clinical guideline on: 'safe and effective prescribing of strong opioids in palliative care of adults'.

3 Clinical need for the guideline

3.1 Current practice

a) Each year more than 155,000 people in the UK die of cancer, and to this figure can be added deaths from heart failure, kidney, liver and respiratory disease, and from neurodegenerative conditions. Many people with these conditions will develop pain for which a strong opioid is needed.

b) The recently updated World Cancer Declaration includes a target to make effective pain control more accessible. Several key documents recognise the importance of effective pain control,

including 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance 2004), 'Control of pain in adults with cancer' (Scottish Intercollegiate Guidelines Network guideline 106), and 'A strategic direction for palliative care services in Wales' (Welsh Assembly Government 2005).

c) Pain is common in advanced and progressive disease. Up to two-thirds of people with cancer experience pain that needs a strong opioid. This proportion is similar or higher in many other advanced and progressive conditions.

d) Strong opioids, especially morphine, are the principal treatments for pain related to advanced and progressive disease, and their use has increased significantly in the primary care setting. However, the pharmacokinetics of the various opioids are very different and there are marked differences in bioavailability, metabolism and response between patients. A suitable opioid must be selected for each patient and, because drug doses cannot be estimated or calculated in advance, the dose must be individually titrated. Ensuring that this selection and titration is done effectively and safely has a major impact on patient comfort. The World Health Organization has produced a pain ladder for the relief of cancer pain and strong opioids are represented on the third level of the three-step ladder.

e) Misinterpretations and misunderstanding have surrounded strong opioids for decades, and these are only slowly being resolved. Until recently, many sources for prescribing advice have given varying and sometimes conflicting advice. These factors, along with the wide range of formulations and preparations, have resulted in errors causing underdosing and avoidable pain, or overdosing and distressing adverse effects. Despite repeated warnings, these problems have led on occasion to patient deaths, and resulted in doctors facing the General Medical Council or court proceedings.

f) This guideline will clarify the clinical pathway, and help to improve pain management and patient safety. The target audience will be non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 years and older) with advanced and progressive disease[1], who require strong opioids for pain control.

b) No patient subgroups have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) Children (younger than 18 years).

b) Adults without advanced and progressive disease.

c) Adults who have not yet had a pain assessment to check whether strong opioids are required.

[1] Such as cancer, heart disease, liver disease, lung disease, kidney disease, HIV and terminal neurodegenerative or neuromuscular conditions.

4.2 Healthcare setting

a) All settings in which care commissioned by the NHS is provided, including hospices, care homes and the community.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) First-line treatment with strong opioids considering:

- titration schedule
- formulation
- routes of administration
- breakthrough pain.

b) Management strategies for side effects (including switching opioid).

c) Information for patients and carers about consenting to treatment and monitoring effectiveness.

4.3.2 Clinical issues that will not be covered

a) Pain assessment before starting strong opioid therapy.

b) Non-opioid pain control.

c) Care during the last days of life (for example, while on the Liverpool Care Pathway).

4.4 Main outcomes

a) Pain.

b) Opioid side effects.

c) Adverse events.

d) Health-related quality of life.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in July 2011.

5 Related NICE guidance

- Neuropathic pain. NICE clinical guideline 96 (2010). Available from www.nice.org.uk/guidance/CG96
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Low back pain. NICE clinical guideline 88 (2009). Available from www.nice.org.uk/guidance/CG88
- Rheumatoid arthritis. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from www.nice.org.uk/guidance/TA159
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008). Available from www.nice.org.uk/guidance/CG75

- Osteoarthritis. NICE clinical guideline 59 (2008). Available from www.nice.org.uk/guidance/CG59
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGSP

6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix D How this guideline was developed

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

The majority of the clinical questions posed in this guideline are interventional questions. For these questions the eligible studies were restricted to randomised controlled trials or systematic reviews thereof. Such studies were included whether they were published in full or as abstracts only. This decision was made in order to include all high level evidence. However, when such evidence was published in abstract form only, full appraisal and reporting of these studies was hampered by a lack of information and this was always highlighted to the GDG. Moreover, due to a lack of evidence, studies that were not on first-line treatment were also included, and when this was the case, it was also highlighted to the GDG.

Search strategies

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2009). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the Information Services Team with advice from the Clinical Guidelines Technical Team. Structured questions were developed using the PICO (population,

intervention, comparison, outcome) model and translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

The NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched for economic evaluations. Search filters for economic evaluations and quality of life studies were used on bibliographic databases. There were no date restrictions imposed on the searches.

Guideline Development Group members were also asked to alert the Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between May 2011 and August 2011.

Guidance/guidelines	**Systematic reviews/economic evaluations**
British Pain Society	Cochrane Database of Systematic Reviews
Cochrane Library	Embase
Embase	Health Economic Evaluations Database
Guidelines and Audit Implementation Network	Medline
Health Technology Assessments	NHS Economic Evaluations Database
Medline	NHS Evidence
National Comprehensive Cancer Network	
National Guideline Clearinghouse (US)	
National Institute for Health and Clinical Excellence (NICE)	
National Institute of Health Research (NIHR)	
NHS Evidence	
Scottish Intercollegiate Guidelines Network	
World Health Organization	

Main searches

The following sources were searched for the topics presented in the sections below.

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (CRD)
- Health Technology Assessment Database – HTA (CRD)
- CINAHL (EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PsycInfo
- Web of Science (Science Citation Index, Social Science Citation Index, ISI Conference Proceedings)

Systematic reviews and mapping searches

The first search was conducted in June 2011 and looked for systematic reviews and primary studies (the 'mapping search' with no methodological filter applied) to answer questions about first line treatment with strong opioids.

The MEDLINE search strategies are presented below. They were translated for use in each of the other databases.

Ovid MEDLINE <1950 to2011>

The patient information search was conducted in May 2011

Information for patients and carers about consenting to treatment and monitoring effectiveness.

Ovid MEDLINE <1950 to 2011>

1. exp Analgesics, Opioid/

2. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
4. (Dipipanone or Pipadone).tw.
5. Exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
7. Hydromorphone/ or (hydromorphon$ or palladone or dilaudid or dihydromorphinone).tw.
8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
9. Methadone/ or (methadone or dolophine).tw.
10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
11. Oxycodone/ or (oxycodone or oxycontin).tw.
12. Oxymorphone/ or (oxymorphone or numorphan).tw.
13. Pentazocine/ or pentazocine.tw.
14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
15. opioid$.tw.
16. or/1-15
17. choice behavior/
18. decision making/
19. exp decision support techniques/
20. ((patient$ or consumer$) adj3 (decision$ or choice or preference or participation)).tw.
21. ((personal or interpersonal or individual) adj3 (decision$ or choice or preference$ or participat$)).tw.
22. (decision$ adj3 (aid$ or support$)).tw.
23. or/17-22
24. exp Patient Participation/
25. Pamphlets/
26. exp Audiovisual Aids/
27. (video$1 or dvd$).tw.

28. exp Internet/
29. exp Self-Help Groups/
30. (support$ adj2 (group$ or meet$)).tw.
31. exp Patient Education/mt
32. ((inform$ or support$) adj2 (tool$ or method$ or group$)).tw.
33. or/24-32
34. (information adj2 (need$ or support$).tw.
35. (information adj2 (leaflet$ or booklet$ or pack$ or material$)).tw.
36. 34 or 35
37. 23 or 33 or 36
38. 16 and 37

First-line treatment with strong opioids considering:

- titration schedule
- formulation
- routes of administration
- breakthrough pain.

1. exp Analgesics, Opioid/
2. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
4. (Dipipanone or Pipadone).tw.
5. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
7. Hydromorphone/ or (hydromorphon$ or palladone or dilaudid or dihydromorphinone).tw.
8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
9. Methadone/ or (methadone or dolophine).tw.
10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.

11. Oxycodone/ or (oxycodone or oxycontin).tw.
12. Oxymorphone/ or (oxymorphone or numorphan).tw.
13. Pentazocine/ or pentazocine.tw.
14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
15. (opioid$ or opiate$).tw.
16. or/1-15
17. breakthrough pain.tw.
18. spontaneous pain.tw.
19. incident$ pain.tw.
20. ((transitory or transient) adj pain).tw.
21. episodic pain.tw.
22. or/17-21
23. 16 and 22

1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
5. Oxycodone/ or (oxycodone or oxycontin).tw.
6. (opioid$ or opiate$).tw.
7. or/1-6
8. exp Chemistry, Pharmaceutical/
9. formulat$.tw.
10. ((immediate or non-sustained) adj2 release).tw.
11. Delayed-Action Preparations/
12. ((sustained or modified or slow or controlled or continuous or prolonged or extended) adj release).tw.
13. or/8-12
14. 7 and 13

1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
5. Oxycodone/ or (oxycodone or oxycontin).tw.
6. (opioid$ or opiate$).tw.
7. or/1-6
8. exp Administration, Oral/
9. exp Administration, Cutaneous/
10. exp Infusions, Subcutaneous/
11. (transdermal or trans-dermal or patch$ or cream$ or ointment$ or unguent$).tw.
12. ((percutaneous or dermal or cutaneous or skin or topical$ or transcutaneous or trans-cutaneous) adj2 (administ$ or deliver$ or route$ or method$)).tw.
13. ((oral$ or mouth) adj2 (administ$ or deliver$ or route$ or method$)).tw.
14. ((subcutaneous$ or infusion$ or implant$ or hypoderm$ or parenteral$) adj2 (administ$ or deliver$ or route$ or method$)).tw.
15. or/8-14
16. 7 and 15

1. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
2. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
3. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
4. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
5. Oxycodone/ or (oxycodone or oxycontin).tw.
6. (opioid$ or opiate$).tw.
7. or/1-6

8. exp Administration, Oral/
9. exp Administration, Cutaneous/
10. exp Infusions, Subcutaneous/
11. (transdermal or trans-dermal or patch$ or cream$ or ointment$ or unguent$).tw.
12. ((percutaneous or dermal or cutaneous or skin or topical$ or transcutaneous or trans-cutaneous) adj2 (administ$ or deliver$ or route$ or method$)).tw.
13. ((oral$ or mouth) adj2 (administ$ or deliver$ or route$ or method$)).tw.
14. ((subcutaneous$ or infusion$ or implant$ or hypoderm$ or parenteral$) adj2 (administ$ or deliver$ or route$ or method$)).tw.
15. or/8-14
16. 7 and 15

Management strategies for side effects (including switching opioid).

nausea and vomiting:

1. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
2. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
3. (Dipipanone or Pipadone).tw.
4. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
5. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
6. Hydromorphone/ or (hydromorphon$ or palladone or dilaudid or dihydromorphinone).tw.
7. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
8. Methadone/ or (methadone or dolophine).tw.
9. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
10. Oxycodone/ or (oxycodone or oxycontin).tw.
11. Oxymorphone/ or (oxymorphone or numorphan).tw.

12. Pentazocine/ or pentazocine.tw.
13. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
14. (opioid$ or opiate$).tw.
15. or/1-14
16. exp Antiemetics/
17. (antiemetic$ or anti emetic$ or anti-emetic$ or anti-nause$ or anti nause$ or emetogen$).tw.
18. 16 or 7
19. 15 and 18

drowsiness:

1. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
2. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
3. (Dipipanone or Pipadone).tw.
4. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
5. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
6. Hydromorphone/ or (hydromorphon$ or palladone or dilaudid or dihydromorphinone).tw.
7. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
8. Methadone/ or (methadone or dolophine).tw.
9. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
10. Oxycodone/ or (oxycodone or oxycontin).tw.
11. Oxymorphone/ or (oxymorphone or numorphan).tw.
12. Pentazocine/ or pentazocine.tw.
13. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
14. (opioid$ or opiate$).tw.
15. or/1-14
16. Lethargy/

17. (drows$ or sleepiness or sleepy or letharg$ or somnolen$ or sluggish or indolen$).tw.
18. 16 or 17
19. 15 and 18

constipation:

1. exp Analgesics, Opioid/
2. Alfentanil/ or (alfentanil or alfentanyl or alphentanyl or alphentanil or rapifen).tw.
3. Buprenorphine/ or (buprenorphine or subutex or buprenex or temgesic).tw.
4. (Dipipanone or Pipadone).tw.
5. exp Fentanyl/ or (fentanyl or fentanil or phentanyl or phentanil or durogesic or sublimaze).tw.
6. Heroin/ or (heroin or diamorphine or diacetylmorphine or diagesil).tw.
7. Hydromorphone/ or (hydromorphon$ or palladone or dilaudid or dihydromorphinone).tw.
8. Meperidine/ or (Meperidine or Demerol or dolantin or pethidine or dolsin).tw.
9. Methadone/ or (methadone or dolophine).tw.
10. exp Morphine/ or (morphine or morphia or MS contin or oramorph or duramorph).tw.
11. Oxycodone/ or (oxycodone or oxycontin).tw.
12. Oxymorphone/ or (oxymorphone or numorphan).tw.
13. Pentazocine/ or pentazocine.tw.
14. (remifentanil or remifentanyl or remiphentanyl or remiphentanil).tw.
15. (opioid$ or opiate$).tw.
16. or/1-15
17. exp Laxatives/
18. (laxative$ or laxation).tw.
19. purgative$.tw.
20. aperient$.tw.
21. cathartic$.tw.
22. (evacuative$ or evacuant$).tw.

23. costive$.tw.
24. (bulking agent$ or osmotic agent$ or enterokinetic agent$).tw.
25. ((stool$ or faecal or fecal) adj soften$).tw.
26. or/17-25
27. 16 and 26

Economic search

The following sources were searched to identify economic evaluations and quality of life data featuring the patient population of Topic 1.

- Medline
- Embase
- NHSEED
- HTA
- HEED

Search of economic-sepcific database:

The first search was conducted in June 2011 and looked for economic studies to answer questions about first line treatment with strong opioids (Topic 1).

The NHS-EED and HTA search strategies are presented below. They were translated for use in HEED.

Not date restriction have been applied to NHS-EED, HTA and HEED.

1. Analgesics, Opioid
   or Opioid Analgesics
   or Opioids
2. Alfentanil
   or Alfentanil Hydrochloride
   or Esteve Brand of Alfentanil Hydrochloride
   or ICI Brand of Alfentanil Hydrochloride
   or Janssen Brand of Alfentanil Hydrochloride
3. Buprenorphine

or Buprenorphine Hydrochloride

or Essex Brand of Buprenorphine Hydrochloride

or Grünenthal Brand of Buprenorphine

or Grünenthal Brand of Buprenorphine Hydrochloride

or Key Brand of Buprenorphine Hydrochloride

or Reckitt & Colman Brand 1 of Buprenorphine Hydrochloride

or Reckitt & Colman Brand 2 of Buprenorphine Hydrochloride

or Reckitt Benckiser Brand of Buprenorphine Hydrochloride

or Reckitt Brand of Buprenorphine Hydrochloride

or Schering-Plough Brand of Buprenorphine Hydrochloride

4. Heroin

or APS Brand of Heroin Hydrochloride

or Evans Vaccines Brand of Heroin Hydrochloride

or Heroin Hydrochloride

5. Fentanyl

or Cephalon Brand of Fentanyl Buccal OraVescent

or Fentanyl Citrate

or Janssen Pharmaceutica Brand of Fentanyl

6. Hydromorphone

or Hydromorphone Hydrochloride

7. Meperidine

or Meperidine Hydrochloride

8. Methadone

or addiCare Brand of Methadone Hydrochloride

or Biomet Brand of Methadone Hydrochloride

or Esteve Brand of Methadone Hydrochloride

or Generics Brand of Methadone Hydrochloride

or GlaxoSmithKline Brand of Methadone Hydrochloride

or Mallinckrodt Brand of Methadone Hydrochloride

or Martindale Brand of Methadone Hydrochloride

or Methadone Hydrochloride

or Pharmascience Brand of Methadone Hydrochloride

or Pinewood Brand of Methadone Hydrochloride

or Rosemont Brand of Methadone Hydrochloride

or Roxane Brand of Methadone Hydrochloride
or Yamanouchi Brand of Methadone Hydrochloride

9. Morphine
or Morphine Chloride
or Morphine Sulfate
or Morphine Sulfate (2:1), Anhydrous
or Morphine Sulfate (2:1), Pentahydrate

10. Oxycodone
or Oxycodone Hydrochloride

11. Oxymorphone
or Bristol-Myers Squibb Brand of Oxymorphone Hydrochloride
or Endo Brand of Oxymorphone Hydrochloride
or Oxymorphone Hydrochloride

12. Pentazocine
or Pentazocine Hydrochloride
or Pentazocine Lactate

13. Remifentanil
or remifentanyl
or remiphentanyl
or remiphentanil

Review questions and review protocols

Review questions

- **What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.**

- **What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?**

- Is immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or transdermal patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?

- Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance therapy for pain in patients with advanced and progressive disease who require strong opioids?

- Is transdermal fentanyl patches more effective than transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?

- Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?

- Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?

- What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?

- **What is the most effective management of side effects of strong opioids?**

- Is laxative treatment more effective with or without opioid switching in reducing constipation in patients with advanced and progressive disease who are taking strong opioids and experience constipation as a side effect?

- Is anti-emetic treatment more effective with or without opioid switching in reducing nausea in patients with advanced and progressive disease who are taking strong opioids and experience nausea as a side effect?

- Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?

Review protocols

Review question 1	What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.
Objectives	To ascertain what information patients and carers have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.
Inclusion/Exclusion criteria	This question is a qualitative question and the evidence was therefore focused on qualitative studies reporting information that patients and/or carers have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.

How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. Additional databases will include: CINAHL and PsycInfo. An animals studies filter will be applied.
The review strategy	The best evidence will come from qualitative studies reporting information that patients have found to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.
POPULATION	Adult patients with advanced and progressive disease who need strong opioids or their carers
SITUATION	Information needs associated with consenting to opioid treatment and monitoring the effectiveness and side effects of the opioid.
TIMING	At the time of considering consenting to opioid treatment and during strong opioid therapy.
OUTCOMES	Information reported by patients/carers to be useful/not useful or wanted/not wanted when considering consenting to opioid treatment and when undergoing treatment with strong opioids.

Review question 2a	Is immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or transdermal patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?
Objectives	To estimate the effectiveness of immediate-release morphine/oxycodone versus sustained-release morphine/oxycodone or versus fentanyl/buprenorphine patches .
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or

	systematic reviews of RCTs comparing immediate-release morphine/oxycodone either to sustained-release morphine/oxycodone or to fentanyl/buprenorphine patches in patients with advanced and progressive disease who require strong opioids for pain.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line immediate-release morphine/oxycodone to first-line sustained-release morphine/oxycodone, and fentanyl/buprenorphine patch, respectively, for pain in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to IR and SR drug (morphine, oxycodone), patch (fentanyl, buprenorphine) and population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids for pain and who are suitable for oral opioid treatment.
INTERVENTION	Immediate release opioid (morphine/oxycodone)
COMPARATORS	Sustained release opioid (morphine or oxycodone) Patch formulation (Fentanyl/ Buprenorphine)
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2b	Is sustained-release morphine more effective than sustained-release

	oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance therapy for pain in patients with advanced and progressive disease who require strong opioids?
Objectives	To estimate the effectiveness of sustained-release morphine versus sustained-release oxycodone or versus fentanyl/buprenorphine patches .
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing sustained-release morphine either to sustained-release oxycodone or to fentanyl/buprenorphine patches in patients with advanced and progressive disease who require strong opioids for pain.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line sustained-release morphine to first-line sustained-release oxycodone, fentanyl patch and buprenorphine patch, respectively, for pain in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are suitable for oral opioid treatment.
INTERVENTION	Sustained release morphine
COMPARATORS	Sustained release oxycodone Fentanyl patch Buprenorphine patch

OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life Percentage of people who achieve pain relief with no/minor side effects/adverse events, -Percentage of people who achieve pain relief with moderate side effects/adverse events, -Percentage of people who do not achieve pain relief with no/minor side effects/adverse events, - Percentage of people who do not achieve pain relief with severe side effects/adverse events.

Review question 2c	Is transdermal fentanyl patches more effective than transdermal buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of fentanyl patches versus buprenorphine patches.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing fentanyl patches to buprenorphine patches in patients with advanced and progressive disease who require strong opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line fentanyl patches to buprenorphine patches for pain in a randomised population. If feasible,

	the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Fentanyl patch
COMPARATORS	Buprenorphine patch
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2d	Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of subcutaneous morphine versus subcutaneous diamorphine and/or subcutaneous oxycodone.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing subcutaneous morphine to subcutaneous diamorphine or to subcutaneous oxycodone in patients with advanced and progressive disease who require strong opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.

The review strategy	The best evidence will come from controlled trials or systematic reviews comparing first-line subcutaneous morphine to first-line subcutaneous diamorphine and/or subcutaneous oxycodone, for pain in a randomised population of patients with advanced and progressive disease who require strong opioids but are not suitable for oral opioid treatment. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Subcutaneous morphine
COMPARATORS	Subcutaneous diamorphine Subcutaneous oxycodone
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2e	Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and who are not suitable for oral treatment?
Objectives	To estimate the effectiveness of the best patch opioid (as established in question 1c) versus the best subcutaneous opioid (as established in question 1d).
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing the best patch opioid to

	the best subcutaneous opioid in patients with advanced and progressive disease who require strong opioids for pain and who are not suitable for oral treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing the best first-line patch (as shown in question 1c) to the best first-line subcutaneous opioid (as shown in question 1d) for pain in a randomised population of patients with advanced and progressive disease who require strong opioids but are not suitable for oral opioid treatment. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.
INTERVENTION	Best patch
COMPARATORS	Best Subcutaneous
OUTCOMES	Pain Opioid side effects Adverse events Percentage of people who switch opioid Health-related quality of life

Review question 2f	What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?
Objectives	To estimate the effectiveness of immediate-release morphine versus fast-acting fentanyls and immediate-

	release oxycodone.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing immediate-release morphine to fast-acting fentanyls or to immediate-release oxycodone in patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with strong opioids for background pain
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials or systematic reviews comparing immediate-release morphine to fast-acting fentanyls or immediate-release oxycodone, respectively, for breakthrough pain in a randomised population of patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with strong opioids for background pain. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the fentanyl preparation (buccal, sublingual, intranasal, transmucosal) and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease who experience breakthrough pain and who are currently treated with first-line opioids for background pain
INTERVENTION	Immediate release morphine
COMPARATORS	Fast acting fentanyl (buccal, sublingual, intranasal, transmucosal) Immediate release (oral) oxycodone
OUTCOMES	Breakthrough pain Background pain?

	Opioid side effects Adverse events Health-related quality of life

Review question 3a	Is laxative treatment with or without opioid switching more effective in reducing constipation in patients with advanced and progressive disease on strong opioids who experience constipation as a side effect?
Objectives	To estimate the effectiveness of laxative treatment + opioid switch versus laxative treatment in patients with advanced and progressive disease who experience constipation from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing laxative treatment + opioid switch to laxative treatment in patients with advanced and progressive disease who experience constipation as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials comparing laxatives with and without an associated switch in the strong opioid used for background pain relief in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the type of laxative used and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids who experience constipation.
INTERVENTION	Laxative + switching opioid

COMPARATORS	Laxative
OUTCOMES	Constipation Treatment compliance Pain

Review question 3b	Is anti-emetic treatment with or without opioid switching more effective in reducing nausea in patients with advanced and progressive disease on strong opioids who experience nausea as a side effect?
Objectives	To estimate the effectiveness of anti-emetic treatment + opioid switch versus anti-emetic treatment in patients with advanced and progressive disease who experience nausea from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing anti-emetic treatment + opioid switch to anti-emetic treatment in patients with advanced and progressive disease who experience nausea as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials comparing anti-emetics with and without an associated switch in the strong opioid used for background pain relief in a randomised population. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the type of anti-emetic used and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids

	who experience nausea.
INTERVENTION	Anti-emetic + switching opioid
COMPARATORS	Anti-emetic
OUTCOMES	Nausea Vomiting Treatment compliance Pain

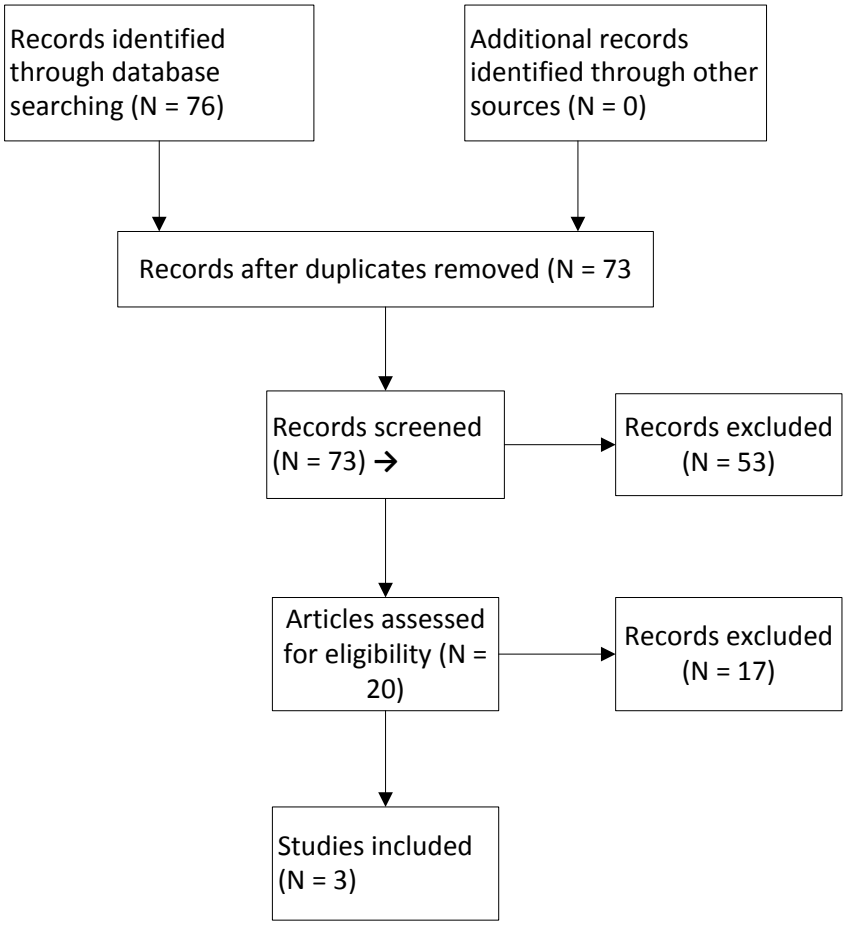
Review question 3c	Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?
Objectives	To estimate the effectiveness of opioid dose reductions versus opioid switching in patients with advanced and progressive disease who experience drowsiness from treatment with strong opioids.
Inclusion/Exclusion criteria	This question is an interventional question and the evidence was therefore restricted to RCTs or systematic reviews of RCTs comparing opioid dose reductions to opioid switches in patients with advanced and progressive disease who experience drowsiness as a side effect of strong opioid treatment.
How the information will be searched	Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.
The review strategy	The best evidence will come from controlled trials that compare opioid dose reductions with opioid switching in randomised populations. If feasible, the data from the included trials will be meta-analysed with potential subgroup analyses performed according to the amount of dose reduction and the population (cancer, non-cancer).
POPULATION	Patients with advanced and progressive disease on strong opioids who experience drowsiness.

INTERVENTION	Reduce dose of opioid
COMPARATORS	Switch opioid
OUTCOMES	Drowsiness Treatment compliance Pain

Excluded studies

Flow diagram of excluded studies for review Question 1

What information do patients with advanced and progressive disease who require strong opioids, or their carers need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid.



Excluded studies

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Excl reason: Patient information material

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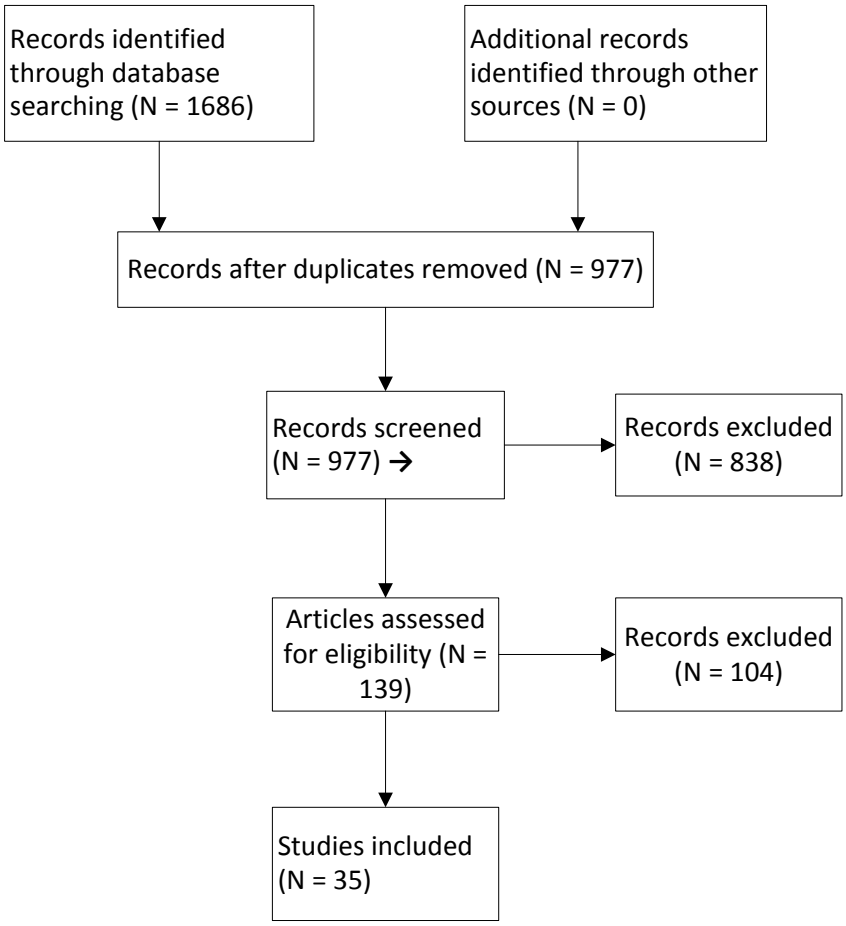
Flow diagram of excluded studies for review Question 2

What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?



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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: In SR by Bekkering 2011 and Tassinari 2008

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Excl reason: Already included in Bekkering et al., and in Tassinari et al. (2008) 2B

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Excl reason: Not in PICO

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Excl reason: Not RCT

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Excl reason: SR of prospective cohort studies in Chinese populations only

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Excl reason: Duplicate

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Excl reason: Not RCT

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Excl reason: Not in PICO

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Excl reason: Not RCT

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO/not RCT

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Excl reason: Not RCT

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Excl reason: Not RCT

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Excl reason: Not RCT

Zeppetella, G. and Ribeiro, M. D. C. Pharmacotherapy of cancer-related episodic pain. Expert Opinion on Pharmacotherapy 4[4], 493-502. 2003.
Excl reason: Narrative review

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Excl reason: Not in PICO: Fentanyl buccal tablet v placebo; Check?

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Excl reason: Duplicate

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Excl reason: Not in PICO

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Excl reason: Not RCT

Zuurmond, W., Davis, C., and Vergidis, D. Transdermal fentanyl shows a similar safety and efficacy profile in elderly and non-elderly patients with cancer pain. SO: Annals of Oncology 13[Suppl 5], 171. 2002.
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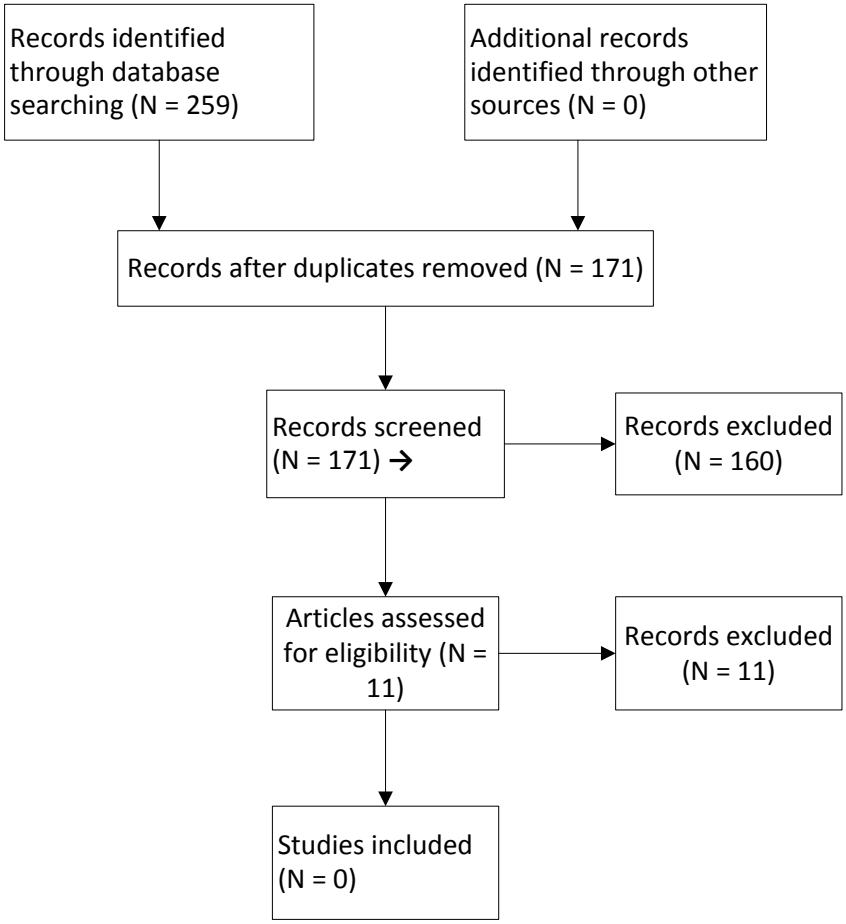
Excl reason: Duplicate

Flow diagram of excluded studies for review Question 3

What is the most effective management of side effects of strong opioids?



Excluded studies

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Duplicate

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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO/Not RCT

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Excl reason: Narrative review

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Excl reason: Not in PICO

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Excl reason: Not in PICO

Blonsky, R. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic non-malignant pain. Journal of Pain Conference[var.pagings], S52. 2009.
Excl reason: Not in PICO

Bradshaw, M. and Sen, A. Use of a prophylactic antiemetic with morphine in acute pain: randomised controlled trial. SO: Emergency medicine journal : EMJ 23[3], 210-213. 2006.
Excl reason: Not in PICO

Bruera, E., Belzile, M., Neumann, C., Harsanyi, Z., Babul, N., and Darke, A. A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. Journal of Pain and Symptom Management 19[6], 427-435. 2000.
Excl reason: Not in PICO

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Excl reason: SR, but no data synthesis. Analyses not in PICO.

Chamberlain, B. Laxative use in patients with advanced illness and opioidinduced constipation treated with subcutaneous methylnaltrexone. Palliative Medicine Conference[var.pagings], S129. 2010.
Excl reason: Not in PICO

Chamberlain, B. H., Cross, K., Winston, J. L., Thomas, J., Wang, W., Su, C., Israel, R. J., Chamberlain, Bruce H., Cross, Karen, Winston, Jaron L., Thomas, Jay, Wang, Wenjin, Su, Chinyu, and Israel, Robert J. Methylnaltrexone treatment of opioid-induced constipation in patients with advanced illness. Journal of Pain & Symptom Management 38[5], 683-690. 2009.
Excl reason: Not in PICO

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Excl reason: (Analyses) not in PICO

Chang, A. K. B. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: A prospective, randomized, double-blind clinical trial. American Journal Geriatric Pharmacotherapy 7[1], 1-10. 2009.
Excl reason: Not in PICO

Chen, T. Y. and Rosow, C. E. Methylnaltrexone bromide. Drugs of the Future 32[9], 771-775. 2007.
Excl reason: Not in PICO

Cherasse, A., Muller, G., Ornetti, P., Piroth, C., Tavernier, C., Maillefert, J. F., Cherasse, Anne, Muller, Geraldine, Ornetti, Paul, Piroth, Christine, Tavernier, Christian, and Maillefert, Jean Francis. Tolerability of opioids in patients with acute pain due to nonmalignant musculoskeletal disease. A hospital-based observational study. Joint, Bone, Spine: Revue du Rhumatisme 71[6], 572-576. 2004.
Excl reason: Not RCT

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Excl reason: Not in PICO for topic 2, but SR? TOPIC1?

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Excl reason: Not in PICO/Not RCT

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Excl reason: Narrative review

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Excl reason: Not in PICO

Crownover, B. Methylnaltrexone (Relistor) for opioid-induced constipation. American Family Physician 82[6]. 2010.
Excl reason: Not in PICO

Cryer, B. L. K. A phase 3, randomized, double-blind, placebo-controlled clinical trial of lubiprostone for the treatment of opioid-induced bowel dysfunction in patients with chronic, non-cancer pain. Gastroenterology Conference[var.pagings], S129. 2010.
Excl reason: Not in PICO

Cubero, D. I. G. Early switching from morphine to methadone is not improved by acetaminophen in the analgesia of oncologic patients: A prospective, randomized, double-blind, placebo-controlled study. Supportive Care in Cancer 18[2], 235-242. 2010.
Excl reason: Not in PICO (acetaminophen = paracetamol)

Culebras. The antiemetic efficacy of droperidol added to morphine patient-controlled analgesia: A randomized, controlled, multicenter dose-finding study (vol 97, pg 816, 2003). Anesthesia and Analgesia 98[1], 88. 2004.
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Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

Diego, L. Methylnaltrexone: A novel approach for the management of opioid-induced constipation in patients with advanced illness. Expert Review of Gastroenterology and Hepatology 3[5], 473-485. 2009.
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Excl reason: Not in PICO

Duerden, M. Subcutaneous methylnaltrexone improves bowel movement frequency and quality in patients with chronic non-malignant pain and opioid induced constipation. Journal of Pain Conference[var.pagings], S46. 2010.
Excl reason: Not in PICO

Duerden, M. Efficacy of subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in subgroups of patients with chronic, nonmalignant pain. Journal of General Internal Medicine Conference[var.pagings], June. 2010.
Excl reason: Not in PICO

Dy, S. M. and Apostol, C. C. Evidence-based approaches to other symptoms in advanced cancer. Cancer Journal from Scientific American 16[5], 507-513. 2010.
Excl reason: Not in PICO

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effectiveness analysis. Alimentary Pharmacology & Therapeutics 31[8], 911-921. 2010.
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Excl reason: Not in PICO

Fleming, V. A review of laxative therapies for treatment of chronic constipation in older adults. American Journal Geriatric Pharmacotherapy 8[6], 514-550. 2010.
Excl reason: Not in PICO

Foss, J. How safe and effective is methylnaltrexone for the treatment of opioid-induced constipation in advanced illness? Nature Clinical Practice Gastroenterology & Hepatology 6[1], 12-13. 2009.
Excl reason: Not in PICO

Foss, J. F. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. American Journal of Surgery 182[5A], 19S-26S. 2001.
Excl reason: Not in PICO

Fredheim, O. M. S. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: A nine-month follow-up study. Palliative Medicine 20[1], 35-41. 2006.
Excl reason: Not in PICO

Freedman, M. D. S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial. Journal of Clinical Pharmacology 37[10], 904-907. 1997.
Excl reason: Population not in PICO

Friedman, J. D. D. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. Annals of Pharmacotherapy 35[1], 85-91. 2001.
Excl reason: Not in PICO

Galvin, E., Boesjes, H., Hol, J., Ubben, J. F., Klein, J., Verbrugge, S. J., Galvin, E., Boesjes, H., Hol, J., Ubben, J. F., Klein, J., and Verbrugge, S. J. C. Modafinil reduces patient-reported tiredness after sedation/analgesia but does not improve patient psychomotor skills. Acta Anaesthesiologica Scandinavica 54[2], 154-161. 2010.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Goodarzi, M. and Goodarzi, M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. Paediatric Anaesthesia 9[5], 419-422. 1999.
Excl reason: Not in PICO

Greenwald, P. W. P. Low-dose naloxone does not improve morphine-induced nausea, vomiting, or pruritus. American Journal of Emergency Medicine 23[1], 35-39. 2005.
Excl reason: Not in PICO

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Excl reason: Comparison not in PICO

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Excl reason: Not in PICO (laxative v laxative)/Not RCT

Healy, R. Effectiveness of two opioid antagonists in treating opioid-induced constipation. British journal of nursing (Mark Allen Publishing) 18[16], 998-1002. 2009.
Excl reason: Not in PICO

Herndon, C. M., Jackson, K. C., and Hallin, P. A. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacotherapy 22[2], 240-250. 2002.
Excl reason: Narrative review

Herndon, C. M. J. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacotherapy 22[2 I], 240-250. 2002.
Excl reason: Narrative review

Holzer, P. Opioid antagonists for prevention and treatment of opioid-induced gastrointestinal effects. Current Opinion in Anaesthesiology 23[5], 616-622. 2010.
Excl reason: Not in PICO

Ilias, W. Patient-controlled analgesia in chronic pain patients: Experience with a new device designed to be used with implanted programable pumps. Pain Practice 8[3], 164-170. 2008.
Excl reason: Not in PICO/Not RCT

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Excl reason: Not in PICO

Iskedjian, M., Iyer, S., Librach, S. L., Wang, M., Farah, B., and Berbari, J. Methylnaltrexone in the Treatment of Opioid-Induced Constipation in Cancer Patients Receiving Palliative Care: Willingness-to-Pay and Cost-Benefit Analysis. Journal of Pain and Symptom Management 41[1], 104-115. 2011.
Excl reason: Not in PICO

Iyer S. Effect of subcutaneous (SC) methylnaltrexone on generic health related quality of life using the eq-5d index scores in patients with chronic non-malignant pain and opioid-induced constipation. Value in Health Conference[var.pagings], A348-A349. 2009.
Excl reason: Not in PICO

Jansen, J. P., Lorch, D., Langan, J., Lasko, B., Hermanns, K., Kleoudis, C. S., Snidow, J. W., Pierce, A., Wurzelmann, J., Mortensen, E. R., Jansen, Jan Peter, Lorch, Daniel, Langan, John, Lasko, Ben, Hermanns, Kai, Kleoudis, Christi S., Snidow, Jerry W., Pierce, Amy, Wurzelmann, John, and Mortensen, Eric R. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. Journal of Pain 12[2], 185-193. 2011.
Excl reason: Not in PICO

Johnson, D. A. Treating chronic constipation: How should we interpret the recommendations? Clinical Drug Investigation 26[10], 547-557. 2006.
Excl reason: Not in PICO

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therapy.Cochrane Database of Systematic Reviews: Protocols 2008 [1]. 2008. John Wiley & Sons, Ltd.
Excl reason: Protocol

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