Clinical Guideline

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

Appendix D – How this guideline was developed
May 2012

Developed for NICE by the National Collaborating Centre for Cancer
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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.

<table>
<thead>
<tr>
<th>Guidance/guidelines</th>
<th>Systematic reviews/economic evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Pain Society</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>Embase</td>
</tr>
<tr>
<td>Embase</td>
<td>Health Economic Evaluations Database</td>
</tr>
<tr>
<td>Guidelines and Audit Implementation</td>
<td>Medline</td>
</tr>
</tbody>
</table>
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>
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 durimaze).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 remiphentany or remiphenanil).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
24. exp Chemistry, Pharmaceutical/
25. formulat$.tw.
26. ((immediate or non-sustained) adj2 release).tw.
27. Delayed-Action Preparations/
28. ((sustained or modified or slow or controlled or continuous or prolonged or extended) adj release).tw.
29. or/8-12
30. 7 and 13
31. exp Administration, Oral/
Management strategies for side effects (including switching opioid).

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

<table>
<thead>
<tr>
<th>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.</th>
</tr>
</thead>
</table>

### 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.

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### Review question 2a

<table>
<thead>
<tr>
<th>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?</th>
</tr>
</thead>
</table>

### 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
### 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.
<table>
<thead>
<tr>
<th>How the information will be searched</th>
<th>Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The review strategy</td>
<td>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).</td>
</tr>
<tr>
<td>POPULATION</td>
<td>Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.</td>
</tr>
<tr>
<td>INTERVENTION</td>
<td>Fentanyl patch</td>
</tr>
<tr>
<td>COMPARATORS</td>
<td>Buprenorphine patch</td>
</tr>
</tbody>
</table>
| OUTCOMES                            | Pain
Opioid side effects
Adverse events
Percentage of people who switch opioid
Health-related quality of life |

**Review question 2d**

<table>
<thead>
<tr>
<th>Where 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?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
</tr>
<tr>
<td>To estimate the effectiveness of subcutaneous morphine versus subcutaneous diamorphine and/or subcutaneous oxycodone.</td>
</tr>
<tr>
<td>Inclusion/Exclusion criteria</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>How the information will be searched</td>
</tr>
<tr>
<td>Databases to be searched will include: Cochrane Library, Medline, Embase, Web of Science. An RCT filter will be applied to the search.</td>
</tr>
<tr>
<td>The review strategy</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>
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).
<table>
<thead>
<tr>
<th>POPULATION</th>
<th>Patients with advanced and progressive disease who require strong opioids and who are not suitable for oral opioid treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION</td>
<td>Best patch</td>
</tr>
<tr>
<td>COMPARATORs</td>
<td>Best Subcutaneous</td>
</tr>
</tbody>
</table>
| 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 from treatment with strong opioids.

**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

<table>
<thead>
<tr>
<th><strong>Review question 3b</strong></th>
<th>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?</th>
</tr>
</thead>
</table>

#### 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

<table>
<thead>
<tr>
<th><strong>Review question 3c</strong></th>
<th>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?</th>
</tr>
</thead>
</table>

#### 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).

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>Patients with advanced and progressive disease on strong opioids who experience drowsiness.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION</td>
<td>Reduce dose of opioid</td>
</tr>
<tr>
<td>COMPARATORS</td>
<td>Switch opioid</td>
</tr>
<tr>
<td>OUTCOMES</td>
<td>Drowsiness                                      Treatment compliance</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
</tbody>
</table>
**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.

Records identified through database searching (N = 76) → Additional records identified through other sources (N = 0) → Records after duplicates removed (N = 73)

Records screened (N = 73) → Records excluded (N = 53) → Articles assessed for eligibility (N = 20) → Records excluded (N = 17) → Studies included (N = 3)

**Excluded studies:**


Intervention reduces chronic pain visits. ED Management 22[12], 141-142. 2010. Excl reason: Not in PICO.


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Guideline

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Coker, E. 6 themes described patients' information needs related to patient controlled analgesia. Evidence Based Nursing 6[3], 93. 2003.
Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Patient information leaflet with no referenced evidence base

Excl reason: Not in PICO

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Patient information material

Excl reason: Not in PICO

Given, B. A. and Sherwood, P. A nurse led educational intervention for cancer pain management was effective in cancer patients in ambulatory settings. Evidence Based Nursing 8[1], 17. 2005.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Patient information material

Excl reason: Not in PICO

Excl reason: Patient information material. 1 patient's questions w/ answer from from doctor
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Scott, D. G. I. In the days of patients' choice, why is the patient being ignored? Lancet 366[9482], 287-288. 23-7-2005.
Excl reason: Not in PICO

Excl reason: Patient information material? check

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO


Wilcox, P. J. and Marks, E. Patient empowerment through education. Oncology Nursing Forum 35[3], 505. 2008. Excl reason: Not in PICO

Wills, B. S. H. and Wootton, Y. S. Y. Concerns and misconceptions about pain among Hong Kong Chinese patients with cancer. Cancer Nursing 22[6], 408-413. 1999. Excl reason: Not in PICO

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?

Records identified through database searching (N = 1686) 
Additional records identified through other sources (N = 0)

Records after duplicates removed (N = 977)

Records screened (N = 977) → Records excluded (N = 838)

Articles assessed for eligibility (N = 139) → Records excluded (N = 104)

Studies included (N = 35)

Excluded studies:

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not RCT
Transdermal buprenorphine (Butrans) for chronic pain. Medical Letter on Drugs & Therapeutics 53[1362], 31-32. 18-4-2011.
Excl reason: Not in PICO

Abasolo, L. and Carmona, O. Systematic review are major opioids effective in the treatment of musculoskeletal pain? Medicina Clinica 128[8], 291-301. 2007.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Population not in PICO

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Narrative review


Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Narrative review


Ashburn, M. A., Slevin, K. A., Messina, J., and Xie, F. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. Anesthesia and Analgesia 112[3], 693-702. 2011. Excl reason: Duplicate


Excl reason: Not RCT, not in PICO

Excl reason: Not RCT, not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

transmucosal fentanyl citrate]. [Turkish]. Agri Dergisi 22[3], 103-108. 2010.
Excl reason: Not RCT

Excl reason: Not in PICO: hydromorphone v sustained-release (SR) oxycodone; population?

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: intravenous morphine v morphine; population?


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO: hydromorphone v hydromorphone

Excl reason: Included in Reid et al (2006) 2A

Excl reason: Not in PICO


Carrer, S., Bocchi, A., Candini, M., Donega, L., Tartari, S., Carrer, S., Bocchi, A., Candini, M., Donega, L., and Tartari, S. Short term analgesia based sedation in the Intensive Care Unit:
morphine vs remifentanil + morphine. Minerva Anestesiologica 73[6], 327-332. 2007.
Excl reason: Not in PICO

Excl reason: Not RCT

Cerchietti, L. Morphine mouthwashes for painful mucositis. SO: Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 15[1], 115-116. 2007.
Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate


Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: SR, but analyses not in PICO

Excl reason: Excluded in Cochrane review as 'duplicate version': oral transmucosal fentanyl citrate versus placebo [abstract]

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: efficacy and safety of intranasal fentanyl, following an initial dose-finding titration period


Coluzzi, P. H. S. Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC\sup<sup>&</sup>) and morphine sulfate immediate release (MSIR\sup<sup>&</sup>). Pain 91[1-2], 123-130. 2001. Excl reason: In Cochrane review: Oral transmucosal fentanyl citrate v morphine sulfate immediate release
Coluzzi, P. H. S. Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Douleurs 3[1], 26-35. 2002.
Excl reason: Duplicate of Coluzzi (2001)

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Comment

Excl reason: Comparison not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: double dose of immediate-release morphine at bedtime v single doses of immediate-release morphine

Excl reason: Duplicate

Excl reason: Duplicate

Darwish, M., Tempero, K., Kirby, M., Thompson, J., Darwish, Mona, Tempero, Kenneth, Kirby, Mary, and Thompson, Jeffrey. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1,080 pg versus oral transmucosal fentanyl citrate 1,600 pg and dose proportionality of FEBT 270 to 1,300 microg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. Clinical Therapeutics 28[5], 715-724. 2006.
Excl reason: Not in PICO

Excl reason: Not in PICO

Darwish, M., Kirby, M., Jiang, J. G., Tracewell, W., Robertson, P., Jr., Darwish, Mona, Kirby, Mary, Jiang, John G., Tracewell, William, and Robertson, Philmore Jr. Bioequivalence following buccal and sublingual placement of fentanyl buccal tablet 400 microg in healthy
Excl reason: Not in PICO

Darwish, M., Kirby, M., Robertson, P., Tracewell, W., and Xie, F. Dose proportionality of fentanyl buccal tablet in doses ranging from 600 to 1300 microg in healthy adult subjects: a randomized, open-label, four-period, crossover, single-centre study. Clinical Drug Investigation 30[6], 365-373. 2010.
Excl reason: Population not in PICO

Excl reason: Population not in PICO

Excl reason: Duplicate

Excl reason: Duplicate (Tassinary 2009)

Excl reason: Duplicate

Excl reason: Guideline

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: SR (?), no data synthesis

Excl reason: Not in PICO
Excl reason: Not in PICO  

Excl reason: Not in PICO  

Excl reason: Not RCT  

Excl reason: Duplicate  

Excl reason: Duplicate  

Excl reason: SR, but with no data pooling  

Excl reason: Narrative review  

Excl reason: Not in PICO  

Excl reason: Not in PICO  

Excl reason: Not in PICO  

Excl reason: Not in PICO  

Derby, S., Chin, J., and Portenoy, R. K. Systemic opioid therapy for chronic cancer pain - Practical guidelines for converting drugs and routes of administration. CNS Drugs 9[2], 99-


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Not in PICO

Eiser, N., Denman, W. T., West, C., Luce, P., Eiser, N., Denman, W. T., West, C., and Luce, P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer"
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: intravenous morphine titration v subcutaneous morphine titration in persisting pain exacerbations

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO


Farrar, J. T. A Novel 12-Week Study, with Three Randomized, Double-Blind Placebo-Controlled Periods to Evaluate Fentanyl Buccal Tablets for the Relief of Breakthrough Pain in Opioid-Tolerant Patients with Noncancer-Related Chronic Pain. Pain Medicine 11[9], 1313-1327. 2010. Excl reason: Not in PICO: fentanyl buccal tablet v placebo for breakthrough pain; population?


860-867. 2010. Excl reason: Not in PICO
Freye E. Levy. Effervescent morphine results in faster relief of breakthrough pain in patients compared to immediate release morphine sulfate tablet. Pain Practice 7[4], 324-331. 2007. Excl reason: Not RCT


Excl reason: Comparison not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO


Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO: methadone v morphine; RCT?

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Expert opinion-based guideline

Greco, M. T. M. Pain in cancer patients: Summary results of a five-years project. Ricerca e Pratica 26[3], 95-105. 2010.
Excl reason: Not in PICO (SR 1 and 2), already covered by search (SR 3)

Excl reason: Population not in PICO

Excl reason: Not RCT

Grond S.Zech. Transdermal fentanyl in the long-term treatment of cancer pain: A prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck


Hale, M., Khan, A., Kutch, M., and Li, S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. SO: Current medical research and opinion 26[6], 1505-1518. 2010. Excl reason: Not in PICO


Hanaoka, K., Yoshimura, T., Tomioka, T., Sakata, H., Hanaoka, Kazuo, Yoshimura, Takashi, Tomioka, Tomoyasu, and Sakata, Hideo. [Double-blind parallel-group dose-titration study
Excl reason: Not in PICO

Excl reason: Not in PICO: fentanyl-containing patch: 1-day v 3-day formulations

Excl reason: Duplicate

Excl reason: Duplicate

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO/Not RCT


Hashizume, T. Validity of recommended minimum dose of prior morphine to initiate transdermal fentanyl patch in prescribing information - multicenter survey of on prescriptions by palliative care specialists in Japan. Gan to Kagaku Ryoho [Cancer & Chemotherapy] 34[6], 897-902. 2007. Excl reason: Not in PICO


Howell, J. Pharmacokinetics of 800 mcg of sublingual fentanyl tablets administered as one 800-mcg tablet, two 400-mcg tablets, or four 200-mcg tablets, in healthy volunteers. Journal
Howell, J. Derrick. Pharmacokinetics of 800 mcg of sublingual fentanyl tablets, administered as one 800-mcg tablet, two 400-mcg tablets, or four 200-mcg tablets, in healthy volunteers. Journal of Pain Conference P57. 2011.
Excl reason: Not in PICO

Howell, J. Derrick. Pharmacokinetics of 800 mcg of sublingual fentanyl tablets, administered as one 800-mcg tablet, two 400-mcg tablets, or four 200-mcg tablets, in healthy volunteers. Journal of Pain Conference P57. 2011.
Excl reason: Not in PICO

Excl reason: Not in PICO: Check original RCT? sublingual fentanyl tablets v placebo

Excl reason: Duplicate

Excl reason: Not in PICO

Hoya, Y. Evaluation of analgesic effect and safety of fentanyl transdermal patch for cancer pain as the first line. Supportive Care in Cancer 18[6], 761-764. 2010.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Huttova, D., Gajdos, M., Gazdikova, K., Zemanek, M., Somorovsky, S., and Dzurik, R. Comparison of relative biological availability of two preparations with morphine sulphate after single administration to healthy volunteers. SO: Farmaceuticky Obzor 70[3], 68-73. 2001.
Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

James, I. G. V., O’Brien, C. M., and McDonald, C. J. A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (BuTrans seven-day patches) with buprenorphine sublingual tablets (Temgesic) in patients with osteoarthritis pain. SO: Journal of pain and symptom management 40[2], 266-278. 2010.  
Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: Morphine v placebo, indirect comparison

Excl reason: Not in PICO

Clinical Pharmacology 71[6], 832-843. 2011.
Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: oxycodone+lidocaine v tramadol+lidocaine in relieving acute neuropathic pain

Excl reason: Duplicate

Excl reason: Not in PICO: intranasal fentanyl v placebo

Excl reason: Not in PICO: fentanyl v fentanyl (doses)

Excl reason: Not RCT

Excl reason: Review specific to the USA

Excl reason: Narrative reviews

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review
Kalso E. Morphine and oxycodone hydrochloride in the management of cancer pain. Clinical Pharmacology and Therapeutics 47[5], 639-646. 1990. Excl reason: Not in PICO (not breakthrough pain, IV then IR morphine and oxycodone hydrochloride, RCT)


Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO (osteoarthritis)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO (osteoarthritis)
Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: SR of oxycodone w/o meta-analysis

Excl reason: Population not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: SR on opioid titration; no metaanalysis

Excl reason: Not RCT


Korte, W., Morant, R., Korte, W., and Morant, R. Transdermal fentanyl in uncontrolled cancer pain: titration on a day-to-day basis as a procedure for safe and effective dose finding--a pilot study in 20 patients. Supportive Care in Cancer 2[2], 123-127. 1994. Excl reason: Not RCT


Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Comparator not in PICO

Excl reason: Not in PICO: intranasal fentanyl spray v placebo

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: fentanyl v fentanyl but RCT?

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: sublingual fentanyl v placebo

Excl reason: Not in PICO


Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT/not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Narrative review

Excl reason: Duplicate


Mandema, J. W., Kaiko, R. F., Oshlack, B., Reder, R. F., Stanski, D. R., Mandema, J. W.,
Kaiko, R. F., Oshlack, B., Reder, R. F., and Stanski, D. R. Characterization and validation of a
pharmacokinetic model for controlled-release oxycodone. British Journal of Clinical
Pharmacology 42[6], 747-756. 1996.
Excl reason: Not in PICO

Marcus, D. A., Glick, R. M., Marcus, Dawn A., and Glick, Ronald M. Sustained-release
2004.
Excl reason: Not in PICO

Marier, J. F., Lor, M., Potvin, D., Dimarco, M., Morelli, G., and Saedder, E. A.
Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system
of fentanyl relative to the commercially available reservoir formulation in healthy subjects. SO:
Excl reason: Not in PICO

Marier, J. F., Lor, M., Potvin, D., Dimarco, M., Morelli, G., Saedder, E. A., Marier, Jean
Francois, Lor, Mary, Potvin, Diane, Dimarco, Marika, Morelli, Gaetano, and Saedder, Eva
Aggerholm. Pharmacokinetics, tolerability, and performance of a novel matrix transdermal
delivery system of fentanyl relative to the commercially available reservoir formulation in
Excl reason: Not in PICO

Marier, J. F., Lor, M., Morin, J., Roux, L., Di, Marco M., Morelli, G., Saedder, E. A., Marier,
Jean Francois, Lor, Mary, Morin, Josee, Roux, Lionel, Di Marco, Marika, Morelli, Gaetano,
and Saedder, Eva Aggerholm. Comparative bioequivalence study between a novel matrix
transdermal delivery system of fentanyl and a commercially available reservoir formulation.
Excl reason: Not in PICO

Marier, J. F., Lor, M., Morin, J., Roux, L., Di, Marco M., Morelli, G., Saedder, E. A., Marier,
Jean Francois, Lor, Mary, Morin, Josee, Roux, Lionel, Di Marco, Marika, Morelli, Gaetano,
and Saedder, Eva Aggerholm. Comparative bioequivalence study between a novel matrix
transdermal delivery system of fentanyl and a commercially available reservoir formulation.
Excl reason: Duplicate

associated with osteoarthritis with controlled-release oxycodone tablets in a randomized
Excl reason: Not in PICO: controlled-release oxycodone versus placebo in osteoarthritis

Markenson, J. A., Croft, J., Zhang, P. G., Richards, P., Markenson, Joseph A., Croft, Joseph,
Zhang, P. G., and Richards, Patricia. Treatment of persistent pain associated with
osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical
Excl reason: Not in PICO

Marshall, D. A., Strauss, M. E., Pericak, D., Buitendyk, M., Codding, C., Torrance, G. W.,
Marshall, Deborah A., Strauss, Marcie E., Pericak, Dan, Buitendyk, Melanie, Codding,
Christine, and Torrance, George W. Economic evaluation of controlled-release oxycodone vs
oxycodone-acetaminophen for osteoarthritis pain of the hip or knee. American Journal of
Managed Care 12[4], 205-214. 2006.
Excl reason: Not in PICO

Maves, T. J., Barcellos, W. A., Maves, T. J., and Barcellos, W. A. Management of cancer pain
with transdermal fentanyl: phase IV trial, University of Iowa. Journal of Pain & Symptom
Excl reason: Not in PICO
Excl reason: Not in PICO: SR of oxymorphone (check)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Menahem S. Continuous subcutaneous delivery of medications for home care palliative patients-using an infusion set or a pump? Supportive Care in Cancer 18[9], 1165-1170. 2010.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT


Excl reason: Narrative review

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Narrative review

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Duplicate

Excl reason: Included in Bekkering et al. (2011) oral sustained-release morphine v oral methadone v transdermal fentanyl (for background pain)

313. 2008.  
Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Not in PICO: intranasal fentanyl spray v oral transmucosal fentanyl citrate

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Included in Bekkering et al. (2011) 2A

Excl reason: Not RCT

Mercadante, S., Tirelli, W., David, F., Arcara, C., Fulfaro, F., Casuccio, A., Gebbia, V., Mercadante, Sebastiano, Tirelli, Walter, David, Fabrizio, Arcara, Carlo, Fulfaro, Fabio,
Excl reason: Duplicate

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: hydromorphone v morphine delivered by continuous subcutaneous infusion, population?

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate


Excl reason: Duplicate
Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Expert opinion-based guideline

Excl reason: Not in PICO: Morphine sustained-release v benztpine (active placebo) chronic regional pain of soft tissue or musculoskeletal origin?

Excl reason: Included in Bekkering et al. (2011) 2A

Excl reason: Duplicate

Excl reason: Included in Reid et al. (2006)

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO: buprenorphine transdermal system at 3 different doses v placebo; population?

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Not in PICO
Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO: SR of RCT on methadone

Excl reason: Included in SR by Bekkering 2011
Excl reason: Not in PICO (population)

Excl reason: (Population) not in PICO

Excl reason: Comment

Excl reason: Not in PICO

Excl reason: Comparison not in PICO

Excl reason: Not in PICO (population = chronic pancreatitis 17/18 from alcohol abuse)

Excl reason: Duplicate

Nik Hisamuddin, N. A. R. Comparison of acute pain relief, after intravenous morphine administration, among different ethnic groups who presented with acute abdominal pain in the Emergency Department. Journal of Emergency Medicine, Trauma and Acute Care 8[2], 73-77. 2008.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO (Mix of studies, those relevant included separately)

Excl reason: Not in PICO

Excl reason: Not in PICO: intranasal fentanyl titrated to doses of 50, 100, and 200 lg v placebo (duplicate?)


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Included in Bekkeringet al., 2011. 2B

Pace, M. C., Passavanti, M. B., Grela, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., Aurilio, C., Pace, Maria Caterina, Passavanti, Maria Beatrice, Grela, Elisa, Mazzariello, Luigi, Maisto, Massimo, Barbarisi, Manlio, Baccari, Ena, Sansone, Pasquale, and Aurilio, Caterina. Buprenorphine in long-term control of chronic pain in cancer patients. Frontiers in Bioscience 12, 1291-1299. 2007.
Excl reason: Duplicate

Pace, M. C., Passavanti, M. B., Grela, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., Aurilio, C., Pace, Maria Caterina, Passavanti, Maria Beatrice, Grela, Elisa, Mazzariello, Luigi, Maisto, Massimo, Barbarisi, Manlio, Baccari, Ena, Sansone, Pasquale, and Aurilio, Caterina. Buprenorphine in long-term control of chronic pain in cancer patients. Frontiers in Bioscience 12, 1291-1299. 2007.
Excl reason: 2C, BUT + TRAMADOL - extracted to evidence table, but also included in Tassinari et al., 2008 and Bekkering 2011


Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO/Not RCT

Excl reason: Not in PICO

Penson, R. T., Joel, S. P., Roberts, M., Gloyne, A., Beckwith, S., Slevin, M. L., Penson, Richard T., Joel, Simon P., Roberts, Michael, Gloyne, Anna, Beckwith, Stephen, and Slevin,


Poole, P. J., Veale, A. G., Black, P. N., Poole, P. J., Veale, A. G., and Black, P. N. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Duplicate

Excl reason: Not in PICO: Morphine v morphine (dose differences)

Excl reason: In Cochrane review: Fentanyl v fentanyl

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO: fentanyl buccal tablet v placebo

Excl reason: Not in PICO

Excl reason: Population not in PICO (chronic low back pain)

Excl reason: Not in PICO: Fentanyl Pectin Nasal Spray v placebo for breakthrough pain

Excl reason: Not RCT

Excl reason: Q & A (not in PICO)

Excl reason: Not in PICO

Excl reason: Not in PICO

Przeklasa-Muszyńska, A. Dobrogowski. Transdermal buprenorphine for the treatment of moderate to severe chronic pain: Results from a large multicenter, non-interventional post-marketing study in Poland. Current Medical Research and Opinion 27[6], 1109-1117. 2011.
Excl reason: Not in PICO

Excl reason: Not RCT


Rauck, R., Farrar, J., Homesley, H., and Busch, M. Multicenter, double-blind, randomized comparison of oral transmucosal fentanyl citrate (OTFC) vs. placebo in cancer patients with breakthrough pain. Anesthesiology 87[3], A748. 1997. Excl reason: Not in PICO: oral transmucosal fentanyl citrate (OTFC) vs. placebo; abstract


Rauck, R. Efficacy and tolerability of sublingual fentanyl in opioid-tolerant cancer patients with breakthrough pain: Interim findings from two long-term, phase III multi-centre studies. Pain Practice Conference[var.pagings], March. 2009. Excl reason: Duplicate


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Population not in PICO


Rauck, R. L. B. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. Journal of Opioid Management 2[3], 155-166. 2006. Excl reason: Not in PICO


Reeves, M. Does the provision of pre-prepared morphine solution alter the administration of opioids to patients in the recovery room? SO: Anaesthesia and intensive care 32[1], 31-32. 2004. Excl reason: Not in PICO


Excl reason: Duplicate

Excl reason: Not in PICO: PR Morphone v SR morphine

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not RCT

Excl reason: No meta-analysis and most included studies not in PICO.

Excl reason: Not in PICO

Roland, C. L., Setnik, B., Cleveland, J., and Brown, D. A. Clinical Outcomes During Opioid Titration Following Initiation with or Conversion to Remoxy®, an Extended-Release Formulation of Oxycodone. Postgraduate Medicine 123[4], 148-159. 2011.
Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Narrative review

Roth, S. H., Fleischmann, R. M., Burch, F. X., Dietz, F., Bockow, B., Rapoport, R. J., Rutstein, J., Lacouture, P. G., Roth, S. H., Fleischmann, R. M., Burch, F. X., Dietz, F., Bockow, B.,


Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Schutter, U., Ritzdorf, I., Heckes, B., Schutter, Ulf, I., and Heckes, B. [The transdermal 7-day buprenorphine patch--an effective and safe treatment option, if tramadol or tilidate/naloxone is insufficient. Results of a non-interventional study]. [German]. MMW Fortschrritte der Medizin 152[31-33], 49. 12-8-2010.
Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Not in PICO: adding oxycodone 5 mg/acetaminophen 325 mg combination tablet on time could improve pain in pts already receiving strong opioids v placebo; RCT?

Excl reason: Narrative review

Excl reason: Narrative review


Excl reason: Narrative review

Excl reason: Not in PICO: Fentanyl buccal tablet (FBT) for the treatment of breakthrough pain in opioid-tolerant patients with neuropathic pain v placebo; abstract

Excl reason: Duplicate

Excl reason: Not in PICO: Population? neuropathic pain, Fentanyl buccal tablet v placebo

Excl reason: Not in PICO

Excl reason: Duplicate


Sittl, R. Changes in the prescribed daily doses of transdermal fentanyl and transdermal buprenorphine during treatment of patients with cancer and noncancer pain in germany: Results of a retrospective cohort study. Clinical Therapeutics 27[7], 1022-1031. 2005. Excl reason: Not RCT


Sittl, R. Transdermal buprenorphine in cancer pain and palliative care. Palliative Medicine 20[SUPPL. 1], s25-s30. 2006. Excl reason: Narrative review


Slatkin, N., V. Fentanyl buccal soluble film (FBSF) demonstrates dose-proportional fentanyl exposure and favorable efficacy and tolerability in the management of breakthrough pain in opioid tolerant cancer patients. Pain Practice Conference[var.pagings], March. 2009. Excl reason: Duplicate


2007.
Excl reason: Not in PICO: Fentanyl buccal tablet v placebo

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Not in PICO. SR of mixed study designs

Excl reason: Duplicate

Excl reason: Not in PICO
Exclusion reason: Not in PICO

Exclusion reason: Same data as reported by Stambough 2001

Exclusion reason: Duplicate

Exclusion reason: Duplicate

Exclusion reason: Not in PICO

Exclusion reason: Not in PICO

Exclusion reason: Not in PICO

Exclusion reason: Duplicate

Exclusion reason: Duplicate

Exclusion reason: systematic review, but no formal data synthesis/meta-analysis

Exclusion reason: Not in PICO

Opioids in palliative care: appendix D (May 2012)
Tassinari, D. Systematic review on the role of transdermal fentanyl (TF) for moderate to severe cancer pain: An EPCRC opioid guidelines project. Palliative Medicine Conference[var.pagings], S120. 2010.
Excl reason: SR w/o meta-analysis (abstract)

Excl reason: SR, but no meta-analysis

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO: once-daily OROS hydromorphone ER v placebo in osteoarthritis

Excl reason: Not RCT

Excl reason: Narrative review

Excl reason: Not in PICO

Tessaro, L. Use of oxycodone controlled-release immediately after NSAIDs: A new approach to obtain good pain control. European Review for Medical and Pharmacological Sciences 14[2], 113-121. 2010.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not in PICO: intravenous morphine administration with PCA v continuous infusion morphine in patients with sickle cell disease during vaso-occlusive crisis

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

Excl reason: Duplicate

Excl reason: Not in PICO: fentanyl buccal tablet v oxycodone immediate-release, but population?

Excl reason: Duplicate

Excl reason: Population not in PICO

Excl reason: Not in PICO

Vasisht, N. Fentanyl buccal soluble film (FBSF) offers high absolute bioavailability and demonstrates faster absorption and greater exposure to fentanyl compared to oral transmucosal fentanyl citrate (OTFC). Pain Practice Conference[var.pagings], March. 2009.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Villesen, H. H. B. Pharmacokinetics of morphine and oxycodone following intravenous administration in elderly patients. Therapeutics and Clinical Risk Management 3[5], 961-967. 2007.
Excl reason: Not in PICO

Excl reason: Not RCT
Excl reason: Not in PICO

Excl reason: Not in PICO: intranasal fentanyl spray v oral transmucosal fentanyl citrate lozenge v oral transmucosal fentanyl buccal tablet; HE - check where data meta-analysis is from

Excl reason: Same as Vissers 2010

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Not RCT/Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Wallace, M. S. T. Clinical Trial Results with OROS<sup>®</sup> Hydromorphone. Journal of Pain and Symptom Management 33[2 SUPPL.], S25-S32. 2007.
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO [fentanyl buccal tablet (FBT) or any traditional short-acting opioid (SAO)]

Excl reason: Not in PICO
Excl reason: Not in PICO

Weinstein, S. M., Shi, M., Buckley, B. J., and Kwarcinski, M. A. Multicenter, open-label, prospective evaluation of the conversion from previous opioid analgesics to extended-release hydromorphone hydrochloride administered every 24 hours to patients with persistent moderate to severe pain. Clinical Therapeutics 28[1], 86-98. 2006.
Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: Duplicate

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Duplicate and not RCT

Westerling, D., Frigren, L., and Hoglund, P. Morphine pharmacokinetics and effects on salivation and continuous reaction times in healthy volunteers. SO: THER DRUG MONIT
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Wiffen, P. J. M. Oral morphine for cancer pain. Cochrane database of systematic reviews (Online) [4], CD003868.2007.
Excl reason: Previous version of an updated Cochrane review

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not RCT


Yoshimoto, T. Efficacy and safety of compound oxycodone injection for cancer pain relief-a multicenter survey of prescriptions. Gan to Kagaku Ryoho Cancer & chemotherapy. 37[5], 871-878. 2010. Excl reason: Not RCT


Flow diagram of excluded studies for review Question 3

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

Records identified through database searching (N = 259) → Additional records identified through other sources (N = 0) → Records after duplicates removed (N = 171) → Records screened (N = 171) → Records excluded (N = 160) → Articles assessed for eligibility (N = 11) → Records excluded (N = 11) → Studies included (N = 0)

Excluded studies

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Duplicate

Excl reason: Not in PICO

Excl reason: Duplicate

Opioids in palliative care: appendix D (May 2012)
Symptom Management 34[5], 547-565. 2007.
Excl reason: Not in PICO

Excl reason: Not in PICO/Not RCT

Benyamin, R. Opioid complications and side effects. Pain Physician 11[SPEC. ISS. 2], S105-S120. 2008.
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Candy, B. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. Cochrane database of systematic reviews (Online) 1[pp CD003448], 2011. 2011.
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

Excl reason: Not in PICO

Excl reason: (Analyses) not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Narrative review/expert opinion

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

Excl reason: Not in PICO/Not RCT

Clemens, K. E. K. Managing opioid-induced constipation in advanced illness: Focus on methylnaltrexone bromide. Therapeutics and Clinical Risk Management 6[1], 77-82. 2010.
Excl reason: Narrative review

Excl reason: Not in PICO

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

Excl reason: Not in PICO

Excl reason: Not in PICO (acetaminophen = paracetamol)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

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


Garnock-Jones, K. P. M. Methylnaltrexone. Drugs 70[7], 919-928. 2010. Excl reason: Not in PICO


Hardy, J., Daly, S., McQuade, B., Albertsson, M., Chimontsi, Kypriou, V, Stathopoulos, P., and Curtis, P. A double-blind, randomised, parallel group, multinational, multicentre study comparing a single dose of ondansetron 24 mg p.o. with placebo and metoclopramide 10 mg t.d.s. p.o. in the treatment of opioid-induced nausea and emesis in cancer patients. Supportive Care in Cancer 10[3], 231-236. 2002. Excl reason: Comparison not in PICO


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


Excl reason: Not in PICO

Ilías, 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

Excl reason: Not in PICO

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

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Protocol

Excl reason: Not in PICO

Excl reason: Not in PICO


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

McNamara, P. Opioid switching from morphine to transdermal fentanyl for toxicity reduction in palliative care. Palliative Medicine 16[5], 425-434. 2002.
Excl reason: Not RCT

Excl reason: Not RCT

Excl reason: SR (of all study types), but with no data synthesis

Excl reason: Not in PICO

Excl reason: (Comparison) Not in PICO

Excl reason: Not in PICO


Miles, C. L. F. Laxatives for the management of constipation in palliative care patients. Cochrane Database of Systematic Reviews[4]. 2006. Excl reason: Not in PICO


Moksnes, K. How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial. Palliative Medicine Conference[variable page], S23-S24. 2010. Excl reason: Comparison (two ways of switching) not in PICO


Ohlen, K. The effect of polyethylene glycol in the treatment of chronic constipation is insufficiently evaluated: A systematic literature review. Lakartidningen 101[34], 2568-2572. 2004. Excl reason: Not in PICO


Perkins, P. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane database of systematic reviews (Online) [2], CD006271. 2009. Excl reason: Not in PICO


Randazzo, B. P. D. Characteristics of gastrointestinal adverse events in patients with opioid-induced constipation and chronic non-malignant pain treated with subcutaneous methylnaltrexone. Gastroenterology Conference[var.pagings], S167. 2010. Excl reason: Not in PICO

Reimer, K., Hopp, M., Zenz, M., Maier, C., Holzer, P., Mikus, G., Bosse, B., Smith, K., Buschmann-Kramm, C., and Leyendecker, P. Meeting the Challenges of Opioid-Induced
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Schiller, L. R. New and emerging treatment options for chronic constipation. Reviews in Gastroenterological Disorders 4[SUPPL. 2], S43-S51. 2004.
Excl reason: Not in PICO/Narrative review

Excl reason: Not in PICO/Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO/Narrative review

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Comparison & intervention not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO/Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Tassinari, D. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: A meta-analysis and systematic review of the literature.
Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Thomas, J. Analysis of response to methylnaltrexone by response to previous dose in patients with advanced illness and opioidinduced constipation. Palliative Medicine Conference[var.pagings], S129-S130. 2010.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not RCT

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Webster, Lynn, Jansen, Jan Peter, Peppin, John, Lasko, Ben, Irving, Gordon, Morlion, Bart, Snidow, Jerry, Pierce, Amy, Mortensen, Eric, Kleoudis, Christi, and Carter, Eric. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: Results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain 137[2], 428-
Excl reason: Not in PICO

Weinstein, S. M., Shi, M., Buckley, B. J., Kwarcinski, M. A., Weinstein, Sharon M., Shi, Minggao, Buckley, Barbara J., and Kwarcinski, Monica A. Multicenter, open-label, prospective evaluation of the conversion from previous opioid analgesics to extended-release hydromorphone hydrochloride administered every 24 hours to patients with persistent moderate to severe pain. Clinical Therapeutics 28[1], 86-98. 2006.
Excl reason: Not in PICO

Excl reason: Population not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review
Yuan, C. S., Foss, J. F., O'Connor, M., Osinski, J., Karrison, T., Moss, J., Roizen, M. F.,
Excl reason: Not in PICO

Yuan, C. S., Foss, Joseph F., O'Connor, Michael, Karrison, Theodore, Osinski, Joachim,
Excl reason: Not in PICO/Not RCT

Excl reason: Not in PICO

Excl reason: Population not in PICO