

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.

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	Medline

Network	
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 alphentanil 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 alphentanil 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-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 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 fentanyl 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 fentanyl 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 fentanyl 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

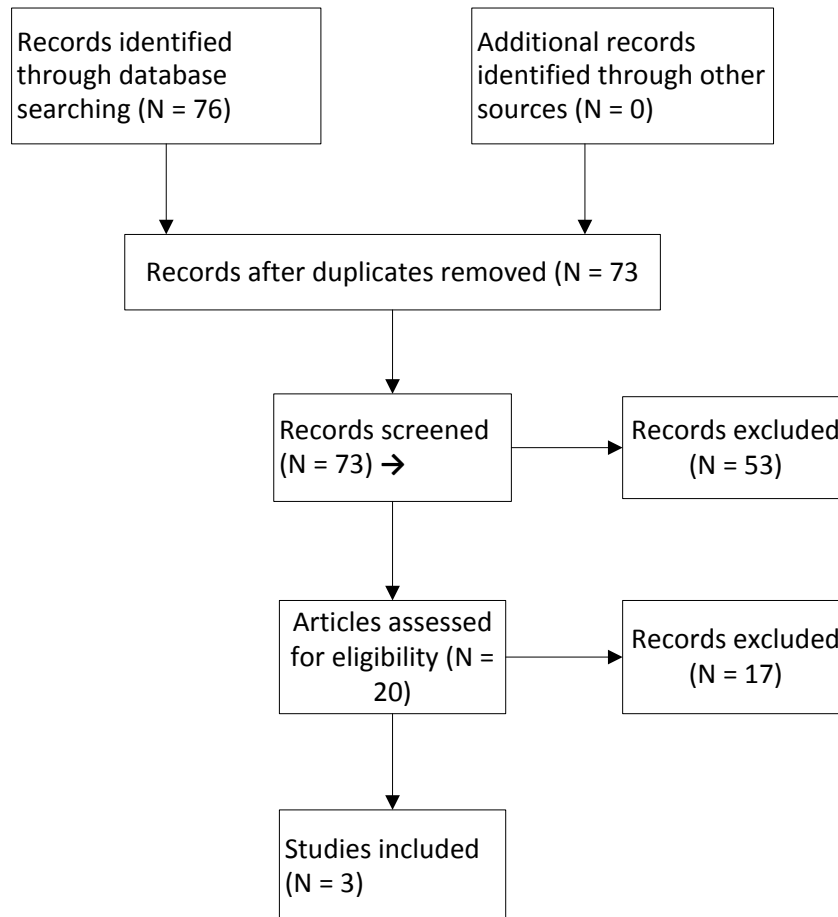
Review question 3c	Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?
Objectives	To estimate the effectiveness of opioid dose reductions versus opioid switching 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:

Questions and answers about pain control: a guide for people with cancer and their families. -76. 1995. Rockville, MD, United States Department of Health and Human Services Public Health Service.

Excl reason: Patient information material

Information from your family doctor. Chronic pain medicines. American Family Physician 69[5], 1197-1198. 1-3-2004.

Excl reason: Patient information on internet with no referenced evidence base.

Intervention reduces chronic pain visits. ED Management 22[12], 141-142. 2010.

Excl reason: Not in PICO

Alonso Herreros, J. M., Najera Perez, M. D., Vazquez, Polo A., Soler, Soler M., and Vila, Clerigues N. Dispensing medical drugs and official preparations to outpatients: Information to the patient. [Spanish]. Farmacia Hospitalaria 20[5], 308-313. 1996.

Excl reason: Not in PICO

Anderson, K. O., Richman, S. P., Hurley, J., Palos, G., Valero, V., Mendoza, T. R., Gning, I., and Cleeland, C. S. Cancer pain management among underserved minority outpatients: Perceived needs and barriers to optimal control. *Cancer* 94[8], 2295-2304. 2002.

Excl reason: Not in PICO

Anderson, K. O., Cohen, M. Z., Mendoza, T. R., Guo, H., Harle, M. T., and Cleeland, C. S. Brief cognitive-behavioral audiotape interventions for cancer-related pain: Immediate but not long-term effectiveness. *Cancer* 107[1], 207-214. 1-7-2006.

Excl reason: Not in PICO

Arnstein, P. Chronic neuropathic pain: issues in patient education. *Pain Management Nursing* 5[4], 34-41. 2-12-2004.

Excl reason: Not in PICO

Aubin, M., Vezina, L., Parent, R., Fillion, L., Allard, P., Bergeron, R., Dumont, S., and Giguere, A. Impact of an educational program on pain management in patients with cancer living at home. *Oncology Nursing Forum* 33[6], 1183-1188. 2006.

Excl reason: Not in PICO

Barlési, F., Duffaud, F., Doddoli, C., Gimenez, C., Auquier, P., Favre, R., and Kleisbauer, J. P. [Impact of a brochure on pain destined for thoracic oncology patients] [French]. *Presse Medicale* 33[19 pt 1], 1313-1318. 2004.

Excl reason: Not in PICO

Bingel, U., Wanigasekera, V., Wiech, K, Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., and Tracey, I. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Science Translational Medicine* 3[70], 70ra14. 2011.

Excl reason: Not in PICO

Binhas, M., Roudot-Thoraval, F., Thominet, D., Maison, P., and Marty, J. Impact of written information describing postoperative pain management on patient agreement with proposed treatment. *European Journal of Anaesthesiology* 25[11], 884-890. 2008.

Excl reason: Not in PICO

Borgsteede, Sander D., Karapinar-larkit, Fatma, Hoffmann, Emmy, Zoer, Jan, and van den Bemt, Patricia M. L. A. Information needs about medication according to patients discharged from a general hospital. *Patient Education and Counseling* 83[1], 22-28. 2011.

Excl reason: Not in PICO

Bozimowski, Greg. Patient Perceptions of Pain Management Therapy: A Comparison of Real-Time Assessment of Patient Education and Satisfaction and Registered Nurse Perceptions. *Pain Management Nursing* In Press. 2011.

Excl reason: Not in PICO

Buchanan, J., Borland, R., Cosolo, W., Millership, R., Haines, I., Zimet, A., and Zalcborg, J. Patients' beliefs about cancer management. *Supportive Care in Cancer* 4[2], 110-117. 1996.

Excl reason: Not in PICO

Cagle, J. G. and Kovacs, P. J. Education: a complex and empowering social work intervention at the end of life. *Health & Social Work* 34[1], 17-27. 2009.

Excl reason: Not in PICO

Cairns, D., Thomas, L., Mooney, V., and Pace, J. B. A comprehensive treatment approach to chronic low back pain. *Pain* 2[3], 301-308. 1976.

Excl reason: Not in PICO

Capewell, C., Gregory, W., Closs, S., and Bennett, M. Brief DVD-based educational intervention for patients with cancer pain: feasibility study. *Palliative Medicine* 24[6], 616-622. 2010.

Excl reason: Not in PICO

Carlsson, M. E., Strang, P. M., and Nygren, U. Qualitative analysis of the questions raised by patients with gynecologic cancers and their relatives in an educational support group. *Journal of Cancer Education* 14[1], 41-46. 1999.

Excl reason: Not in PICO

Casarett, D., Karlawish, J., Sankar, P., Hirschman, K. B., and Asch, D. A. Obtaining informed consent for clinical pain research: Patients' concerns and information needs. *Pain* 92[1-2], 71-79. 2001.

Excl reason: Not in PICO

Chou, Roger, Fanciullo, Gilbert J., Fine, Perry G., Adler, Jeremy A., Ballantyne, Jane C., Davies, Pamela, Donovan, Marilee I., Fishbain, David A., Foley, Kathy M., Fudin, Jeffrey, Gilson, Aaron M., Kelter, Alexander, Mauskop, Alexander, O'Connor, Patrick G., Passik, Steven D., Pasternak, Gavrill W., Portenoy, Russell K., Rich, Ben A., Roberts, Richard G., Todd, Knox H., and Miaskowski, Christine. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. *The Journal of Pain* 10[2], 113-130. 2009.

Excl reason: Guideline

Chumbley, G. M., Hall, G. M., and Salmon, P. Patient-controlled analgesia: what information does the patient want? *Journal of Advanced Nursing* 39[5], 459-471. 2002.

Excl reason: Not in PICO

Chumbley, G. M., Ward, L., Hall, G. M., and Salmon, P. Pre-operative information and patient-controlled analgesia: much ado about nothing. *Anaesthesia* 59[4], 354-358. 2004.

Excl reason: Not in PICO

Citron, M. L., Kaplan, R., Parris, W. C., Croghan, M. K., Herbst, L. H., Rosenbluth, R. J., Reder, R. F., Slagle, N. S., Buckley, B. J., and Kaiko, R. F. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. *Cancer Investigation* 16[8], 562-571. 1998.

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

Davies, J. and McVicar, A. Balancing efficiency, cost-effectiveness and patient choice in opioid selection. *International Journal of Palliative Nursing* 6[10], 470-478. 2000.

Excl reason: Narrative review

De Simone, G. G. Palliative care in Argentina: perspectives from a country in crisis. *Journal of Pain & Palliative Care Pharmacotherapy* 17[3/4], 23-43. 2003.

Excl reason: Narrative review

De Simone, L. Methadone information for patients and families. *Journal of Palliative Medicine* 10[6], 1437-1438. 2007.

Excl reason: Patient information leaflet with no referenced evidence base

de Wit, R., van Dam, F., Hanneman, M., Zandbelt, L., van Buuren, A., van der Heijden, K., Leenhouts, G., Loonstra, S., and Huijjer Abu-Saad, H. Evaluation of the use of a pain diary in chronic cancer pain patients at home. *Pain* 79[1], 89-99. 1999.

Excl reason: Not in PICO

de Wit, R., van Dam, F., Loonstra, S., Zandbelt, L., van Buuren, A., van der Heijden, K., Leenhouts, G., Duivenvoorden, H., and Huijjer Abu-Saad, H. Improving the quality of pain treatment by a tailored pain education programme for cancer patients in chronic pain. *European Journal of Pain* 5[3], 241-256. 2001.

Excl reason: Not in PICO

de Wit, R. and van Dam, F. From hospital to home care: a randomized controlled trial of a Pain Education Programme for cancer patients with chronic pain. *Journal of Advanced Nursing* 36[6], 742-754. 2001.

Excl reason: Not in PICO

Dechelette, M., Krakowski, I., Arbiol, E., Chvetzoff, G., Cullet, D., Delorme, T., Fontaine, A., Lavillat, D., Marec-Berard, P., Torloting, G., Vuillemin, N., Brusco, S., Carretier, J., Leichtnam-Dugarin, L., Delavigne, V., Fervers, B., and Philip, T. Pain and cancer: Informational materials for cancer patients and their relatives. [French]. *Douleur et Analgesie* 20[4], 272-281. 2007.

Excl reason: Patient information material

Duensing, L., Eksterowicz, N., MacArio, A., Brown, M., Stern, L., and Ogbonnaya, A. Patient and physician perceptions of treatment of moderate-to-severe chronic pain with oral opioids. *Current Medical Research and Opinion* 26[7], 1579-1585. 2010.

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

Goldberg, G. R. and Morrison, R. S. Pain management in hospitalized cancer patients: A systematic review. *Journal of Clinical Oncology* 25[13], 1792-1801. 2007.

Excl reason: Not in PICO

Gunnarsdottir, S., Donovan, H. S., and Ward, S. Interventions to overcome clinician- and patient-related barriers to pain management. *Nursing Clinics of North America* 38[3], 419-434. 2003.

Excl reason: Narrative review

Hockel, M. [Meaningful patient-oriented service! Pharmacy information for pain patients] [German]. *Pharmazie in Unserer Zeit* 31[1], 83-89. 2002.

Excl reason: Not in PICO

Kataoka, T., Sato, T., Hashimoto, S., and Shino, M. [Patient education in cancer pain management with opioids] [Japanese]. *Nippon Rinsho. Japanese Journal of Clinical Medicine* 65[1], 42-48. 2007.

Excl reason: Not in PICO

Krakowski, I., Dechelette, M., Arbiol, E., Chvetzoff, G., Cullet, D., Delorme, T., Fontaine, A., Lavillat, D., Marec-Berard, P., Torloting, G., Vuillemin, N., Brusco, S., Carretier, J., Delavigne, V., Leichtnam-Dugarin, L., Fervers, B., Philip, T., Standards, Options et Recommandations SOR, Ligue contre le Cancer pour la Vie, Institut National, du Cancer, Federation Nationale des Centre, Societe Francaise d'Etude et de Traitement de la Douleur (SFETD), Federation Hospitaliere, de France, Federation Nationale de Cancerologies Centres Hospitaliers Regionaux et Univ, Federation Francaise, de Cancerologie, Union Nationale Hospitaliers Privee de Cancerologie (UNHPC), and Global Cancer Control, UICC. [Pain and cancer Information dedicated to cancer patients and relatives]. [French]. *Bulletin du Cancer* 95[4], 443-448. 2008.

Excl reason: Patient information material

Lambert, K., Oxberry, S., Hulme, C. W., Saharia, K., Rigby, A. S., and Johnson, M. J. Knowledge and attitudes to opioids in palliative care patients. *Palliative Medicine* 21[8], 721-722. 2007.

Excl reason: Not in PICO

Littlejohn, F. C. A patient-oriented exploration of opioid therapy: With special emphasis on methadone's special role. *Journal of Pain & Palliative Care Pharmacotherapy* 23[1], 58-60. 2009.

Excl reason: Patient information material. 1 patient's questions w/ answer from from doctor

Lovell, Melanie R., Forder, Peta M., Stockler, Martin R., Butow, Phyllis, Briganti, Esther M., Chye, Richard, Goldstein, David, and Boyle, Frances M. A Randomized Controlled Trial of a Standardized Educational Intervention for Patients with Cancer Pain. *Journal of Pain and Symptom Management* 40[1], 49-59. 2010.

Excl reason: Not in PICO

Maunsell, E., Allard, P., Dorval, M., and Labbe, J. A brief pain diary for ambulatory patients with advanced cancer: Acceptability and validity. *Cancer* 88[10], 2387-2397. 2000.

Excl reason: Not in PICO

McCarberg, B. H., Nicholson, B. D., Todd, K. H., Palmer, T., and Penles, L. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. *American Journal of Therapeutics* 15[4], 312-320. 2008.

Excl reason: Not in PICO

Mehta, A., Robin Cohen, S., Ezer, H., Carnevale, F. A., and Ducharme, F. Striving to Respond to Palliative Care Patients' Pain at Home: A Puzzle for Family Caregivers. *Oncology Nursing Forum* 38[1], E37-E45. 2011.

Excl reason: Not in PICO

Miyashita, M., Sato, K., Morita, T., and Suzuki, M. Effect of a population-based educational intervention focusing on end-of-life home care, life-prolonging treatment and knowledge about palliative care. *Palliative Medicine* 22[4], 376-382. 2008.

Excl reason: Not in PICO

Oldenmenger, W. H., Sillevs Smitt, P. A. E., van Dooren, S., Stoter, G., and van der Rijt, C. C. D. A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: A critical appraisal. *European Journal of Cancer* 45[8], 1370-1380. 2009.

Excl reason: Not in PICO

Oldman, M., Moore, D., and Collins, S. Drug patient information leaflets in anaesthesia: effect on anxiety and patient satisfaction. *British Journal of Anaesthesia* 92[6], 854-858. 2004.

Excl reason: Not in PICO

Palos, G. R. Opioids and cancer survivors: issues in side-effect management. *Oncology Nursing Forum* 35[6], 13-19. 2-11-2008.

Excl reason: Not in PICO

Ranchere, J. Y., Delfosse, M. H., Saltel, P., and Latour, J. F. Morphine therapy: evaluation of patient information. [French]. *Bulletin du Cancer* 85[4], 353-357. 1998.

Excl reason: Not in PICO

Rimer, B., Keintz, M. K., Levy, M., Engstrom, P. F., and Rodzvic, D. Cancer pain management: a clinical trial of an education program for patients. *Progress in Clinical and Biological Research* 216, 311-317. 1986.

Excl reason: Not in PICO

Rimer, B., Levy, M., Keintz, M. K., MacElwee, N., and Engstrom, P. F. Improving cancer patients' pain control through education. *Progress in Clinical and Biological Research* 248, 123-127. 1987.

Excl reason: Not in PICO

Sand, A. M., Harris, J., and Rosland, J. H. Living with advanced cancer and short life expectancy: Patients' experiences with managing medication. *Journal of Palliative Care* 25[2], 85-91. 2009.

Excl reason: Not in PICO

Schuit, K. W., Cost, Budde P., Van, Heest F., and Rolf, C. Telephone consultation is effective in terminal care. [Dutch]. *Huisarts en Wetenschap* 46[7], 388-391. 2003.
Excl reason: Not in PICO

Schumacher, K. L., West, C., Dodd, M., Paul, S. M., Tripathy, D., Koo, P., and Miaskowski, C. A. Pain management autobiographies and reluctance to use opioids for cancer pain management. *Cancer Nursing* 25[2], 125-133. 2002.
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

Serrie, Alain. Managing pain with strong opioids: practical advice useful to your cancer patients [French]. *Traitements par opioïdes forts : conseils pratiques pour en parler avec vos patients cancéreux. Douleurs : Evaluation - Diagnostic - Traitement* 9[Supplement 1], S1-S10. 2008.
Excl reason: Patient information material? check

Seymour, J. E., Bellamy, G., Gott, M., Ahmedzai, S. H., and Clark, D. Good deaths, bad deaths: older people's assessments of the risks and benefits of morphine and terminal sedation in end-of-life care. *Health Risk & Society* 4[3], 287-303. 2002.
Excl reason: Not in PICO

Shino, M., Eguchi, H., Yoshimoto, F., Yajima, S., Ohguro, M., and Hiraga, K. An analysis of a questionnaire on morphine formulations through the bereaved families. [Japanese]. *IRYO - Japanese Journal of National Medical Services* 48[1], 27-31. 1994.
Excl reason: Not in PICO

Simone, C. B., Vapiwala, N., Hampshire, M. K., and Metz, J. M. Internet-based survey evaluating use of pain medications and attitudes of radiation oncology patients toward pain intervention. *International Journal of Radiation Oncology, Biology, Physics* 72[1], 127-133. 1-9-2008.
Excl reason: Not in PICO

Syrjala, K. L., Abrams, J. R., Polissar, N. L., Hansberry, J., Robison, J., DuPen, S., Stillman, M., Fredrickson, M., Rivkin, S., Feldman, E., Gralow, J., Rieke, J. W., Raish, R. J., Lee, D. J., Cleeland, C. S., and DuPen, A. Patient training in cancer pain management using integrated print and video materials: a multisite randomized controlled trial. *Pain* 135[1-2], 175-186. 2008.
Excl reason: Not in PICO

Theiler, R., Alon, E., Brugger, S., Ljutow, A., Mietzsch, T., Muller, D., Ott, A., Rimle, M., Zemp, A., and Urwyler, A. Evaluation of a standardized internet-based and telephone-based patient monitoring system for pain therapy with transdermal fentanyl. *Clinical Journal of Pain* 23[9], 804-811. 2007.
Excl reason: Not in PICO

Townley, S., Papaleontiou, M., Amanfo, L., Henderson Jr, C. R., Pillemar, K., Beissner, K., and Reid, M. Preparing to Implement a Self-Management Program for Back Pain in New York City Senior Centers: What Do Prospective Consumers Think? *Pain Medicine* 11[3], 405-415. 2010.
Excl reason: Not in PICO

Turunen, J. H. O., Mantyselka, P. T., Ojala, R. K., Kroger, P. O., and Ahonen, R. S. The public's information needs on analgesics: A descriptive study in a drug information centre. *International Journal of Pharmacy Practice* 16[2], 91-97. 2008.
Excl reason: Not in PICO

Ward, S., Hughes, S., Donovan, H., and Serlin, R. C. Patient education in pain control. *Supportive Care in Cancer* 9[3], 148-155. 2001.
Excl reason: Narrative review

Weis, O. F., Sriwatanakul, K., Weintraub, M., and Lasagna, L. Reduction of anxiety and postoperative analgesic requirements by audiovisual instruction. *Lancet* 1[8314-5], 43-44. 1-1-1983.
Excl reason: Not in PICO

Wells, N., Hepworth, J. T., Murphy, B. A., and Wujcik, D. Improving Cancer Pain Management Through Patient and Family Education. *Journal of Pain and Symptom Management* 25[4], 344-356. 2003.
Excl reason: Not in PICO

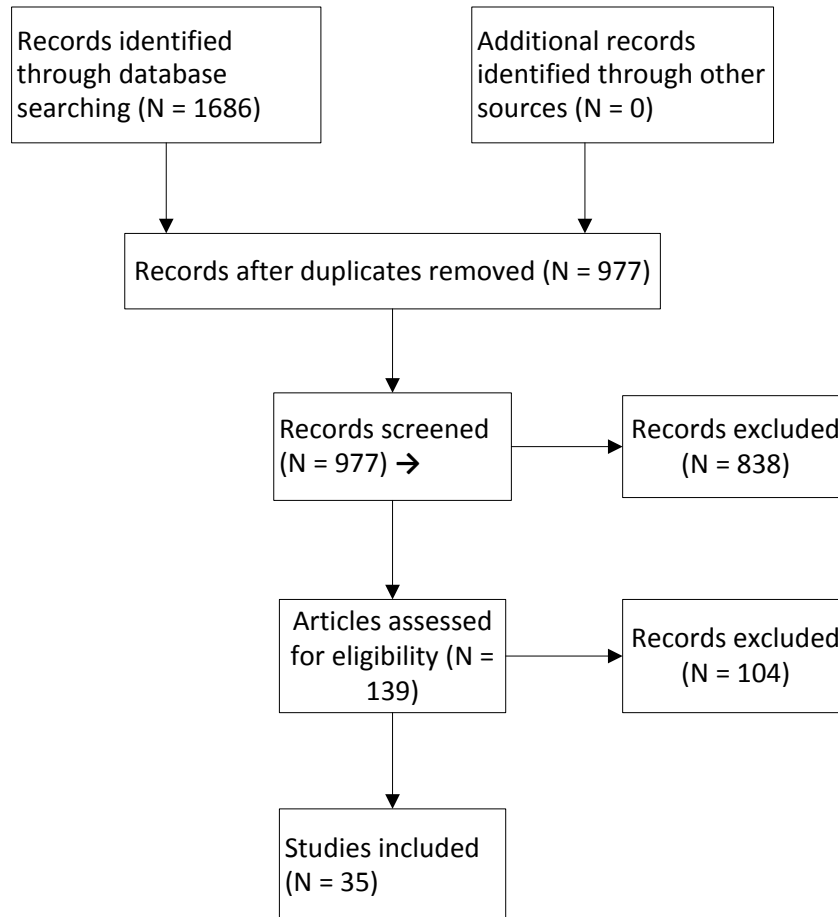
Wilcox, P. J. and Marks, E. Patient empowerment through education. *Oncology Nursing Forum* 35[3], 505. 2008.
Excl reason: Not in PICO

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

Wilsey, B. L., Fishman, S. M., Casamalhuapa, C., and Gupta, A. Documenting and improving opioid treatment: the Prescription Opioid Documentation and Surveillance (PODS) System. *Pain Medicine* 10[5], 866-877. 2009.
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?



Excluded studies:

Transdermal fentanyl (new preparation). Helpful alternative to morphine and to oral and subcutaneous routes. *Prescrire International* 7[37], 137-140. 1998.

Excl reason: Not in PICO

Oral transmucosal fentanyl: new preparation. For breakthrough cancer pain when morphine fails. *Prescrire International* 11[60], 106-107. 2002.

Excl reason: Narrative review

Oral oxycodone: new preparation. No better than oral morphine. *Prescrire International* 12[65], 83-84. 2003.

Excl reason: Narrative review

Fentanyl sublingual tablets (abstral): An opioid analgesic for the management of breakthrough pain in cancer patients. *Formulary* 46[3]. 2011.

Excl reason: Not in PICO

Fentanyl sublingual tablet: A guide to its use in breakthrough pain in opioid-tolerant adults with cancer. *Drugs and Therapy Perspectives* 27[7], 6-9. 2011.

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

Abernethy, A. P., Currow, D. C., Frith, P., Fazekas, B. S., McHugh, A., Bui, C., Abernethy, Amy P., Currow, David C., Frith, Peter, Fazekas, Belinda S., McHugh, Annie, and Bui, Chuong. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 327[7414], 523-528. 6-9-2003.
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: buprenorphine transdermal patch changes every 3 v 4 days

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Excl reason: Not in PICO

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Excl reason: Not in PICO

Wiffen, P. J. E. Oral morphine for cancer pain. *Cochrane database of systematic reviews (Online)* [4], CD003868. 2003.
Excl reason: Duplicate

Wiffen, P. J. E. Oral morphine for cancer pain. *Cochrane database of systematic reviews (Online)* [4], CD003868. 2003.
Excl reason: Previous version of an updated Cochrane review

Wiffen, P. J. M. Oral morphine for cancer pain. *Cochrane database of systematic reviews (Online)* [4], CD003868. 2007.
Excl reason: Cochrane review, updated by Caraceni et al., 2011

Wiffen, P. J. M. Oral morphine for cancer pain. *Cochrane database of systematic reviews (Online)* [4], CD003868. 2007.
Excl reason: Duplicate

Wiffen, Philip J. and McQuay, Henry J. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* [4]. 2007. John Wiley & Sons, Ltd.
Excl reason: Duplicate

Wilding, I. R., Davis, S. S., Rimoy, G. H., Rubin, P., Kurihara, B. T., Tipnis, V., Berner, B., and Nightingale, J. Pharmacokinetic evaluation of transdermal buprenorphine in man. *SO: International Journal of Pharmaceutics*. 132[1-2], 81-87. 1996.
Excl reason: Not in PICO

Wilkinson, T. J., Robinson, B. A., Begg, E. J., Duffull, S. B., Ravenscroft, P. J., and Schneider, J. J. Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients. *SO: Cancer chemotherapy and pharmacology* 31[3], 251-254. 1992.
Excl reason: Not in PICO

William, L. and MacLeod, R. Management of breakthrough pain in patients with cancer. *Drugs* 68[7], 913-924. 2008.
Excl reason: Narrative review

Winklbaaur, B., Ebner, N., Jagsch, R., Thau, K., and Fischer, G. Quality of life in patients undergoing opioid maintenance therapy - A comparative study of slow release morphine versus methadone treatment. *European Psychiatry* 22, S203-S204. 2007.
Excl reason: Not in PICO

Wirz, S., Wartenberg, H. C., Elsen, C., Wittmann, M., Diederichs, M., Nadstawek, J., Wirz, Stefan, Wartenberg, Hans Christian, Elsen, Christian, Wittmann, Maria, Diederichs, Marta, and Nadstawek, Joachim. Managing cancer pain and symptoms of outpatients by rotation to sustained-release hydromorphone: a prospective clinical trial. *Clinical Journal of Pain* 22[9], 770-775. 2006.
Excl reason: Not RCT

Wolff, T., Samuelsson, H., Hedner, T., Wolff, T., Samuelsson, H., and Hedner, T. Concentrations of morphine and morphine metabolites in CSF and plasma during continuous subcutaneous morphine administration in cancer pain patients. *Pain* 68[2-3], 209-216. 1996.
Excl reason: Not in PICO

Wong, J. O., Chiu, G. L., Tsao, C. J., and Chang, C. L. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *SO: Acta anaesthesiologica Sinica* 35[1], 25-32. 1997.
Excl reason: In SR by Bekkering 2011 and Tassinari 2008

Wong, J. O., Chiu, G. L., Tsao, C. J., Chang, C. L., Wong, J. O., Chiu, G. L., Tsao, C. J., and Chang, C. L. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain.[Erratum appears in *Acta Anaesthesiol Sin* 1007 Sep;35(3):191]. *Acta Anaesthesiologica Sinica* 35[1], 25-32. 1997.
Excl reason: Already included in Bekkering et al., and in Tassinari et al. (2008) 2B

Wong, M. C., Chung, J. W., and Wong, T. K. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review (Structured abstract). *BMJ* 335, 87. 2007.
Excl reason: Not in PICO

Worrich, S., Schuler, G., Janicki, P. K., Worrich, Scott, Schuler, Gregg, and Janicki, Piotr K. Effect of local administration of transdermal fentanyl on peripheral opioid analgesia. *Pain Medicine* 8[1], 41-47. 2007.
Excl reason: Not in PICO

Wu, X.-N. Zhao. Clinical efficacy and safety of oxycontin in 85 patients with moderate and severe cancer pain. *Chinese Journal of New Drugs* 18[8], 710-713. 2009.
Excl reason: Not RCT

Xu, D. F. Prospective and long-term follow-up study on morphine sulphate controlled-release tablets in the treatment of cancer pain. *European Journal of Pain-London* 5, 123. 2001.
Excl reason: Not in PICO

Xu, G. Z., Cai, Z. J., Deng, Y. P., hou, J., Xie, G. R., and Liu, S. J. Clinical evaluation of the analgesic effect of sustained release morphine sulfate microgranules in patients with terminal cancer. *Clinical Drug Investigation* 14, 34-42. 1997.
Excl reason: Not in PICO

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Excl reason: Japanese - cannot extract data

Yang, Q., Xie, D. R., Jiang, Z. M., Ma, W., Zhang, Y. D., Bi, Z. F., and Chen, D. L. Efficacy and adverse effects of transdermal fentanyl and sustained-release oral morphine in treating moderate-severe cancer pain in Chinese population: a systematic review and meta-analysis (Provisional abstract). *Journal of Experimental and Clinical Cancer Research* 29[1]. 2010.
Excl reason: SR of prospective cohort studies in Chinese populations only

Yang, Q., X. Efficacy and adverse effects of transdermal fentanyl and sustained-release oral morphine in treating moderate-severe cancer pain in Chinese population: a systematic review and meta-analysis. *Journal of experimental & clinical cancer research : CR* 29[pp 67], 2010. 2010.
Excl reason: Duplicate

Yanni, L. Baseline demographic data from OPUS: The Opioid Utilization Study in chronic noncancer pain. *Journal of Pain Conference*[var.pagings], S49. 2009.
Excl reason: Not RCT

Yao, W. X., Zhou, H., Wang, L. Y., Wei, Y., Liu, X. Y., Yao, Wen Xiu, Zhou, Hang, Wang, Li Yang, Wei, Yang, and Liu, Xian Yu. [Efficacy comparison between morphine sulfate controlled-released tablet and morphine hydrochloride sustained-released tablet in treating cancer pain]. [Chinese]. *Aizheng* 26[12], 1357-1359. 2007.
Excl reason: Not in PICO

Yeo, W., Lam, K. K., Chan, A. T., Leung, T. W., Nip, S. Y., Johnson, P. J., Yeo, W., Lam, K. K., Chan, A. T., Leung, T. W., Nip, S. Y., and Johnson, P. J. Transdermal fentanyl for severe cancer-related pain. *Palliative Medicine* 11[3], 233-239. 1997.
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

Yu, S. Y., Qiu, H., Ma, Z. S., Chen, J., Zhang, Y., Chen, L. Z., Wang, D. L., Ma, Z. Y., Yu, Shi Ying, Qiu, Hong, Ma, Zhen shan, Chen, Jia, Zhang, Ying, Chen, Li zheng, Wang, Dong lin, and Ma, Zhi yong. [Effects of sustained release morphine hydrochloride tablets in management of cancer pain: a survey of 567 patients]. [Chinese]. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 84[6], 450-455. 17-3-2004.
Excl reason: Not in PICO

Yu, S. Y., OxyContin Tablets Postmarketing Surveillance Study Group, Yu, Shi Ying, and OxyContin Tablets Postmarketing Surveillance Study Group. Postmarketing surveillance study of OxyContin tablets for relieving moderate to severe cancer pain. *Oncology* 74 Suppl 1, 46-51. 2008.
Excl reason: Not in PICO

Zacny, J. P., Gutierrez, S., Zacny, James P., and Gutierrez, Sandra. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. *Psychopharmacology* 170[3], 242-254. 2003.
Excl reason: Not in PICO

Zacny, J. P., Lichtor, S. A., Zacny, James P., and Lichtor, Stephanie A. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers.[Erratum appears in *Psychopharmacology (Berl)*. 2008 Jan;196(1):117]. *Psychopharmacology* 196[1], 105-116. 2008.
Excl reason: Not in PICO

Zacny, J. P. and Lichtor, S. A. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers. *Psychopharmacology* 196[1], 105-116. 2008.
Excl reason: Not in PICO

Zarth, R. Ehmer. Oral transmucosal fentanyl citrate for the treatment of breakthrough pain: Results of a non-interventional study (NIS). *Schmerz* 21[6], 545-552. 2007.
Excl reason: Not RCT

Zautra, A. J., Smith, B. W., Zautra, Alex J., and Smith, Bruce W. Impact of controlled-release oxycodone on efficacy beliefs and coping efforts among osteoarthritis patients with moderate to severe pain. *Clinical Journal of Pain* 21[6], 471-477. 2005.
Excl reason: Not in PICO

Zech, D. F., Lehmann, K. A., Zech, D. F., and Lehmann, K. A. Transdermal fentanyl in combination with initial intravenous dose titration by patient-controlled analgesia. *Anti-Cancer Drugs* 6 Suppl 3, 44-49. 1995.
Excl reason: Not in PICO/not RCT

Zech, D. F. J. Transdermal fentanyl in combination with initial intravenous dose titration by patient-controlled analgesia. *Anti-Cancer Drugs* 6[SUPPL. 3], 44-49. 1995.

Excl reason: Not RCT

Zeppetella, G. An assessment of the safety, efficacy, and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: A pilot study. *Journal of Pain and Symptom Management* 20[4], 253-258. 2000.

Excl reason: Not RCT

Zeppetella, G. Sublingual fentanyl citrate for cancer-related breakthrough pain: a pilot study. *Palliative Medicine* 15[4], 323-328. 2001.

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

Zeppetella, G. Opioids for Cancer Breakthrough Pain: A Pilot Study Reporting Patient Assessment of Time to Meaningful Pain Relief. *Journal of Pain and Symptom Management* 35[5], 563-567. 2008.

Excl reason: Not RCT

Zeppetella, G., Messina, J., Xie, F., Slatkin, N. E., Zeppetella, Giovambattista, Messina, John, Xie, Fang, and Slatkin, Neal E. Consistent and clinically relevant effects with fentanyl buccal tablet in the treatment of patients receiving maintenance opioid therapy and experiencing cancer-related breakthrough pain. *Pain Practice* 10[4], 287-293. 2010.

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

Zeppetella, Giovambattista and Ribeiro, Maria. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database of Systematic Reviews* [1]. 2006.

John Wiley & Sons, Ltd.

Excl reason: Duplicate

Zhang, J.-X. and Zhou, X. Comparison of side effects between China-made transdermal fentanyl and imported Durogesic: A randomized self-crossover controlled trial. *Chinese Journal of New Drugs* 19[3], 262-264. 2010.

Excl reason: Not in PICO

Zhao, Y.-B. Effects of transdermal fentanyl for relieving advanced cancer pain and quality of life in elder patients. *Chinese Journal of Clinical Rehabilitation* 8[26], 5500-5501. 2004.

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.

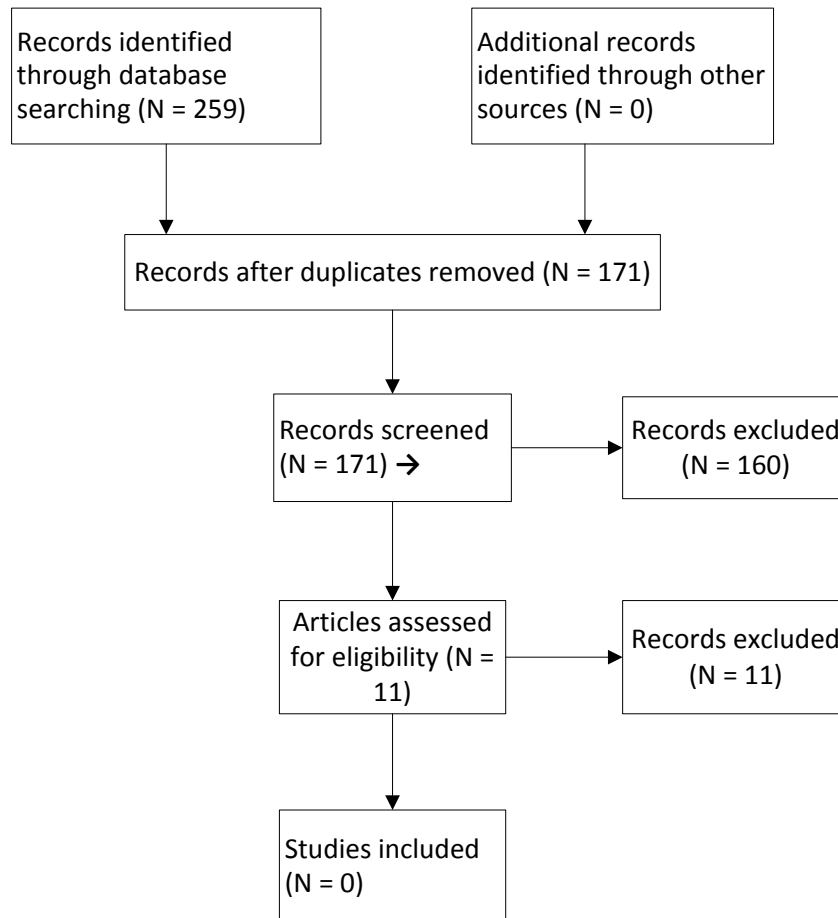
Excl reason: Not in PICO

Zuurmond, W. W. Safety and efficacy of transdermal fentanyl (Durogesic) compared with sustained-release morphine in patients with cancer pain [abstract]. *SO: Proceedings of the American Society of Clinical Oncology* 21 (Pt 1), 377a, Abstract. 2002.

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

Methylnaltrexone: A guide to its use in opioid-induced constipation in patients with advanced illness. *Drugs and Therapy Perspectives* 26[12], 5-8. 2010.

Excl reason: Not in PICO

Agra Varela, Y. A. S. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *Journal of Pain and Symptom Management* 15[1], 1-7. 1998.

Excl reason: Not in PICO

Agra, Y., Sacristan, A., Gonzalez, M., Ferrari, M., Portugues, A., Calvo, M. J., Agra, Y., Sacristan, A., Gonzalez, M., Ferrari, M., Portugues, A., and Calvo, M. J. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *Journal of Pain & Symptom Management* 15[1], 1-7. 1998.

Excl reason: Duplicate

Barrow, P. M., Hughes, D. G., Redfern, N., and Urie, J. Influence of Droperidol on Nausea and Vomiting During Patient-Controlled Analgesia. *British Journal of Anaesthesia* 72[4], 460-461. 1994.

Excl reason: Not in PICO

Becker, G., Galandi, D., and Blum, H. E. Peripherally Acting Opioid Antagonists in the Treatment of Opiate-Related Constipation: A Systematic Review. *Journal of Pain and*

Symptom Management 34[5], 547-565. 2007.
Excl reason: Not in PICO

Bennett, M. Factors influencing constipation in advanced cancer patients: A prospective study of opioid dose, dantrolene dose and physical functioning. *Palliative Medicine* 17[5], 418-422. 2003.
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

Bignell, M. Naloxone hydrochloride sr gastro-resistant sustained release capsules, (Nalcol) as a treatment for functional constipation: A randomised, double blind controlled trial in secondary care - Preliminary results. *Gastroenterology Conference*[var.pagings], S614. 2011.
Excl reason: Not in PICO

Binsfeld, H., Szczepanski, L., Waechter, S., Richarz, U., Sabatowski, R., Binsfeld, Heinrich, Szczepanski, Leszek, Waechter, Sandra, Richarz, Ute, and Sabatowski, Rainer. A randomized study to demonstrate noninferiority of once-daily OROS([REGISTERED]) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. *Pain Practice* 10[5], 404-415. 2010.
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

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 opioid-induced 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

Chan, S. L. Serotonin antagonists for the treatment of opioid-induced nausea and vomiting in non-surgical patients (Structured abstract). *SO: Singapore General Hospital Proceedings* 18[1], 33-38. 2009.
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

Cherny, Nathan, Ripamonti, Carla, Pereira, Jose, Davis, Carol, Fallon, Marie, McQuay, Henry, Mercadante, Sebastiano, Pasternak, Gavril, and Ventafridda, Vittorio. Strategies to Manage the Adverse Effects of Oral Morphine: An Evidence-Based Report. *Journal of Clinical Oncology* 19[9], 2542-2554. 1-5-2001.

Excl reason: Narrative review/expert opinion

Clark, A. J., Ahmedzai, S. H., Allan, L. G., Camacho, F., Horbay, G. L., Richarz, U., Simpson, K., Clark, A. J., Ahmedzai, S. H., Allan, L. G., Camacho, F., Horbay, G. L. A., Richarz, U., and Simpson, K. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Current Medical Research & Opinion* 20[9], 1419-1428. 2004.

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

Clemens, K. E., Quednau, I., and Klaschik, E. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. *International Journal of Clinical Practice* 65[4], 472-478. 2011.

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

Clemens, K. E. M. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: Review of efficacy and safety data in the treatment of patients experiencing chronic pain. *Expert Opinion on Pharmacotherapy* 11[2], 297-310. 2010.

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.
Excl reason: Not in PICO

Davis, M. P. H. A Systematic Review of the Treatment of Nausea and/or Vomiting in Cancer Unrelated to Chemotherapy or Radiation. *Journal of Pain and Symptom Management* 39[4], 756-767. 2010.
Excl reason: Not in PICO

Deibert, P., Xander, C., Blum, H. E., Becker, G., Deibert, Peter, Xander, Carola, Blum, Hubert E., and Becker, Gerhild. Methylnaltrexone: the evidence for its use in the management of opioid-induced constipation. *Core Evidence* 4, 247-258. 2010.
Excl reason: Not in PICO

di Fazano, C. S., Vergne, P., Grilo, R. M., Bertin, P., Bonnet, C., and Treves, R. Preventive therapy or nausea and vomiting in patients on opioid therapy for non malignant pain in rheumatology. *Therapie* 57[5], 446-449. 2002.
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.
Excl reason: Not in PICO

DiPetrillo, L. ALKS 37, A novel, peripherally-restricted opioid receptor antagonist, demonstrates efficacy in the treatment of opioid-induced bowel dysfunction. *Gastroenterology Conference[var.pagings]*, S136. 2011.
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

Earnshaw, S. R., Klok, R. M., Iyer, S., and McDade, C. Methylnaltrexone bromide for the treatment of opioid-induced constipation in patients with advanced illness - a cost-effectiveness analysis. *Alimentary Pharmacology & Therapeutics* 31[8], 911-921. 2010.
Excl reason: Not in PICO

Eisenberg E. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 293[24], 3043-3052. 2005.
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

Garnock-Jones, K. P. M. Methylnaltrexone. *Drugs* 70[7], 919-928. 2010.
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

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

Hawley, P. H. and Byeon, J. J. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *Journal of Palliative Medicine* 11[4], 575-581. 2008.
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 1], 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 programmable pumps. *Pain Practice* 8[3], 164-170. 2008.

Excl reason: Not in PICO/Not RCT

Irving, G., Penzes, J., Ramjattan, B., Cousins, M., Rauck, R., Spierings, E. L., Kleoudis, C. S., Snidow, J. W., Pierce, A., Wurzelmann, J., Mortensen, E. R., Irving, Gordon, Penzes, Janos, Ramjattan, Brian, Cousins, Michael, Rauck, Richard, Spierings, Egilius L. H., Kleoudis, Christi S., Snidow, Jerry W., Pierce, Amy, Wurzelmann, John, and Mortensen, Eric R. A randomized, placebo-controlled phase 3 trial (study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *Journal of Pain* 12[2], 175-184. 2011.

Excl reason: Not in PICO

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Excl reason: Not in PICO

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