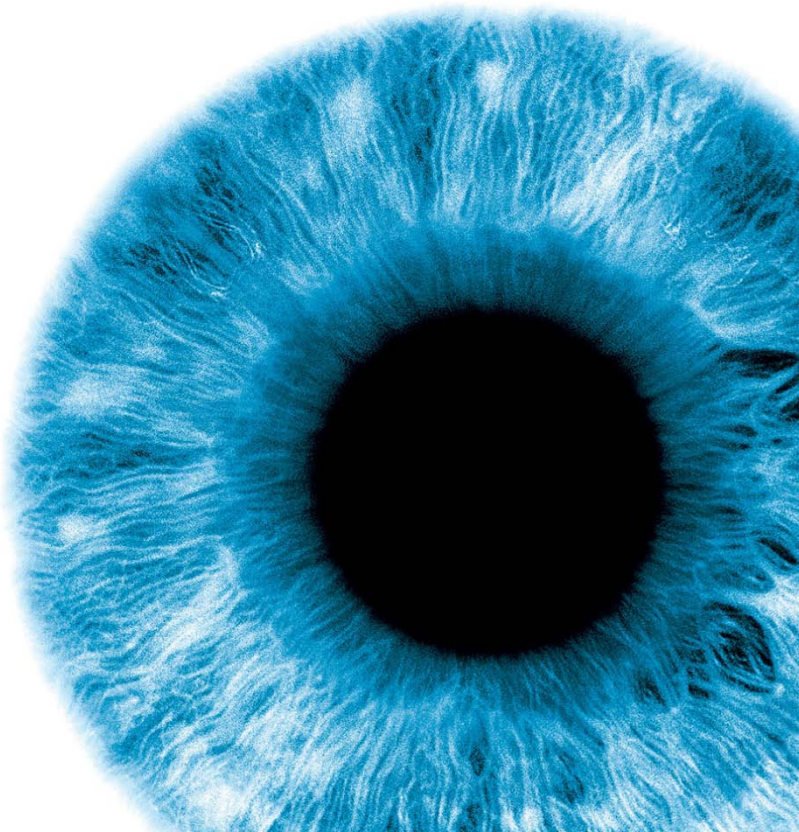
NICE National Institute for Health and Care Excellence

Opioids in palliative care

Evidence Update May 2014

A summary of selected new evidence relevant to NICE clinical guideline 140 'Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults' (2012)

Evidence Update 58



Contents

Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NICE Evidence Services topic page for palliative care.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Opioids in palliative care. NICE clinical guideline 140 (2012)**

A search was conducted for new evidence from 27 May 2011 to 27 November 2013. A total of 4451 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 18 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 5 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 140 (NICE CG140). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guideline development methods for further information about updating clinical guidelines.

NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- Opioids in palliative care. NICE Pathway

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG140. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG140.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Starting strong opioids – titrating the dose • Oral morphine is an effective analgesic for cancer pain, with similar efficacy to other opioids. Titration to analgesic effect appears to be possible for both immediate-release and sustained-release formulations of oral morphine.		✓
First-line treatment if oral opioids are not suitable – transdermal patches • Limited evidence suggests most patients with moderate to severe cancer pain receiving transdermal fentanyl have no worse than mild pain within a reasonably short time period, and experience less constipation compared with oral morphine.		✓
First-line treatment for breakthrough pain in patients who can take oral opioids • Oral and nasal transmucosal fentanyl seem to be effective treatments for breakthrough cancer pain, and appear to be more effective than oral morphine for pain intensity at 15 minutes. However, the benefits of transmucosal fentanyl over oral morphine remain unlikely to outweigh its substantial additional cost.		✓
Management of constipation • Evidence suggests that mu-opioid receptor antagonists appear to be safe and effective treatments for opioid-induced constipation. However, evidence of the efficacy of these drugs in a palliative care setting, particularly when compared with optimised laxative therapy, is limited.		✓

1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Section headings are taken from NICE CG140.

1.1 Communication

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 Starting strong opioids – titrating the dose

Oral morphine for cancer pain

NICE CG140 recommends that when starting treatment with strong opioids, patients with advanced and progressive disease should be offered regular oral sustained-release or oral immediate-release morphine (depending on patient preference).

A Cochrane review by **Wiffen et al. (2013)** assessed oral morphine for cancer pain. Randomised controlled trials (RCT) of more than 10 patients (adults or children) examining oral morphine versus placebo, non-oral morphine, or active control, were eligible. A total of 62 studies were identified (n=4241).

The included studies compared: modified versus immediate-release morphine (15 RCTs); modified release morphine versus other opioids (15 RCTs); different strengths of modified release morphine (14 RCTs); immediate release morphine versus other opioids (6 RCTs); oral versus rectal modified release morphine (2 RCTs); immediate release morphine via different administration routes (2 RCTs); modified release morphine given at different times (2 RCTs); immediate release morphine given at different times (2 RCTs); modified release morphine tablet versus suspension (1 RCT); modified release morphine versus non-opioids (1 RCT), immediate release morphine versus non-opioids (1 RCT); and oral versus epidural morphine (1 RCT). Daily doses in studies ranged from 25 to 2000 mg (average 100–250 mg). Data could not be meta-analysed therefore all analyses were qualitative. The definition of 'no worse than mild pain' used in the review equated to a score of ≤30/100 mm on a visual analogue pain intensity scale, or its equivalent on other pain scales.

An average level of 'no worse than mild pain' was achieved in 18 studies, and no study reported average pain levels above this threshold in patients receiving oral morphine. In the 17 studies reporting results for individual patients, 96% (362/377) of patients had 'no worse than mild pain', and an outcome equivalent to treatment success (or successful pain control, or participant global evaluation of 'very good' or 'excellent') was deemed to have been achieved in 63% (400/638) of patients. Pain relief did not differ between modified and immediate release morphine, and the authors noted that dose titration to analgesic effect was achieved with both these formulations. In 24 studies reporting data on patient withdrawal because of adverse effects, the dropout rate was 7% (154/2162). Among 9 studies reporting patient withdrawals because of ineffective analgesia, the dropout rate was also 7% (41/544).

Limitations of the evidence included that:

- Only 13 of the 62 studies adequately reported randomisation methods, few reported on allocation concealment, and some were not double blind.
- Most studies were considered by the authors to be at high risk of bias because of their size (only 11 studies included at least 100 participants and most had fewer than 50).
- Patient-reported outcomes such as a good level of pain relief were reported in only 9 of 62 studies (although 7 reported other outcomes of value from the patient perspective).

- It was noted that many studies focused on small statistical differences between formulations or opioids, rather than clinically useful outcomes.
- The review authors also noted that pharmaceutical industry sponsorship was explicitly mentioned in 32 studies.

The authors concluded that oral morphine is an effective analgesic for cancer pain, with similar efficacy to other opioids. Titration to analgesic effect appears to be possible for both immediate-release and sustained-release formulations of oral morphine. This evidence is consistent with recommendations in NICE CG140 that patients starting treatment with strong opioids should be offered sustained-release or immediate-release oral morphine depending on preference.

Key reference

Wiffen PJ, Wee B, Moore RA (2013) Oral morphine for cancer pain. Cochrane Database of Systematic Reviews issue 7: CD003868

1.3 First-line maintenance treatment

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.4 First-line treatment if oral opioids are not suitable – transdermal patches

Transdermal fentanyl for cancer pain

NICE CG140 recommends that initiating transdermal patches with the lowest acquisition cost should be considered for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed. Caution should be used when calculating opioid equivalence for transdermal patches:

- A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily.

A Cochrane review by **Hadley et al. (2013)** examined transdermal fentanyl for cancer pain. RCTs of 10 or more participants per treatment arm (adults or children, inpatients or outpatients, with chronic moderate to severe pain) conducted over a minimum of 7 days, were eligible. Studies comparing transdermal fentanyl patches (of any dose, frequency, or duration) with placebo or active controls were included. Pain had to be measured using a validated assessment tool. A total of 9 studies (n=1382) were identified. Within these studies, 600 patients received transdermal fentanyl patches, 382 were given various morphine formulations, 221 received paracetamol plus codeine, and 36 received methadone. Primary outcomes were: patients with pain reduction of at least 30%, and at least 50%, from baseline; patients with no worse than mild pain; and patients 'much improved' or 'very much improved' (or equivalent wording) on the Patient Global Impression of Change scale.

No studies reported on any of the primary outcomes, and insufficient comparable data were available to perform a meta-analysis for any analgesia outcomes. In 7 studies (n=461) reporting pain intensity after 2 weeks, the mean or median pain scores were on the boundary of mild and moderate pain. Fewer participants had constipation with transdermal fentanyl than with oral morphine (28% versus 46%, risk ratio=0.61, 95% confidence interval [CI] 0.47 to 0.78, p=0.000078; 4 studies, n=484). The authors stated that data for other adverse events such as nausea, abdominal pain, gastrointestinal bleeding, and confusion could not be compared meaningfully, as it was difficult to establish the contribution of the underlying disease to these outcomes.

The main limitation of the evidence was the methodological quality of the included studies, which the authors stated was poor overall. For example, only 1 study was double blind, most

studies recruited fewer than 100 participants, and only 1 of the treatment groups was large enough to be at low risk of bias.

The authors concluded that from limited evidence, most patients with moderate to severe cancer pain receiving transdermal fentanyl have no worse than mild pain within a reasonably short time period, and experience less constipation compared with oral morphine. The evidence is consistent with the recommendation in NICE CG140 that transdermal patches (such as fentanyl) should be considered for patients in whom oral opioids are not suitable.

The randomised literature on transdermal fentanyl remains limited, and further research with a greater consistency of study design and reporting (particularly for patient-related outcomes, such as pain reduction to tolerable levels) is needed.

Key reference

Hadley G, Derry S, Moore RA et al. (2013) Transdermal fentanyl for cancer pain. Cochrane Database of Systematic Reviews issue 10: CD010270

1.5 First-line treatment if oral opioids are not suitable – subcutaneous delivery

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.6 First-line treatment for breakthrough pain in patients who can take oral opioids

Opioids for breakthrough pain in cancer

NICE CG140 recommends offering oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment. The guideline further states: do not offer fast-acting fentanyl as first-line rescue medication. In the full version of NICE CG140, it was noted that although the guideline development group was satisfied that there was limited evidence that fentanyl is more clinically effective than immediate-release morphine, it felt the cost impact of recommending fentanyl would be considerable and therefore could not be justified.

A Cochrane review by **Zeppetella et al. (2013)** assessed opioid analgesics for managing breakthrough pain in patients with cancer. RCTs of patients of all ages, in any setting, comparing opioids as rescue medication (any dose or administration route) with active comparator (including other opioids) or placebo, were eligible. A total of 15 studies (n=1699) were identified, all of which reported on transmucosal fentanyl formulations (5 oral and 2 nasal). The included studies assessed: fentanyl versus placebo (8 studies), fentanyl versus another opioid (4 studies), and different doses of the same fentanyl formulation (1 study). The remaining 2 trials were randomised titration studies. Of the 15 included studies, only 2 were of direct relevance to NICE CG140 – 1 study of oral fentanyl versus oral morphine, and 1 study of nasal fentanyl versus oral morphine. Data from both of these trials were examined for the original guideline.

From a meta-analysis of the 2 studies of most relevance to the guideline, for pain intensity difference at 15 minutes, transmucosal fentanyl was more effective than oral morphine (mean difference=0.37, 95% CI 0.00 to 0.73, p=0.048; 2 studies, n=154). Other meta-analyses showed that transmucosal fentanyl was more effective than placebo at 10, 15 and 30 minutes ($p<0.00001$ for all 3 time points).

The main limitation of the evidence was the methodological quality of the included studies: only 7 of the 15 studies were assessed by the authors as being at low risk of bias, 2 studies

were not double blind, and 2 studies were at a high risk of bias because of their size (n=40 and n=27).

The authors concluded that oral and nasal transmucosal fentanyl seem to be effective treatments for breakthrough cancer pain, and appear to be more effective than oral morphine for pain intensity at 15 minutes. However, the benefits of transmucosal fentanyl over oral morphine remain unlikely to outweigh its substantial additional cost – the average cost of treating a breakthrough event with fentanyl was calculated to be approximately 50 times more than with morphine in the full version of NICE CG140. This evidence is therefore unlikely to have an impact on the statement in NICE CG140: do not offer fast-acting fentanyl as first-line rescue medication.

Key reference

Zeppetella G, Davies AN (2013) Opioids for the management of breakthrough pain in cancer patients. Cochrane Database of Systematic Reviews issue 10: CD004311

1.7 Management of constipation

Pharmacological therapies for opioid-induced constipation

NICE CG140 recommends informing patients that constipation affects nearly all patients receiving strong opioid treatment. Laxative treatment should be prescribed (to be taken regularly at an effective dose) for all patients initiating strong opioids, and patients should be informed that treatment for constipation takes time to work and adherence is important. Laxative treatment for managing constipation should be optimised before considering switching strong opioids. The guideline does not currently recommend specific drugs for treatment of constipation.

An RCT (n=185) by **Ahmedzai et al. (2012)** compared effects of oxycodone with or without the addition of naloxone (a mu-opioid receptor antagonist, which when orally administered acts almost exclusively in the gastrointestinal tract) on constipation and analgesia. Patients aged 18 or over, with moderate or severe cancer pain needing round-the-clock opioid therapy, were eligible. Exclusion criteria were: clinically unstable disease or significant cardiovascular, renal, hepatic or psychiatric disease; clinically significant gastrointestinal disease or abnormalities; recent chemotherapy; or radiotherapy (that would influence bowel function or pain) or chemotherapy scheduled within the study period. On entering the study, patients stopped any current opioids and laxatives and were then randomised to prolonged-release tablets comprising either an oxycodone/naloxone combination, or oxycodone alone. All patients were titrated up to a maximum of 120 mg/day oxycodone. Immediate-release oxycodone was available as rescue treatment (maximum 6 doses per 24 hours). Patients needing the maximum daily dose of oxycodone and who regularly needed 2 or more rescue doses were withdrawn from the study. Bisacodyl was available as rescue laxative (maximum 5 doses within 7 days).

The 2 primary outcomes were constipation symptoms on the validated Bowel Function Index (BFI), and chronic cancer pain on the Brief Pain Inventory–Short Form. The authors stated that a change in BFI score of 12 points or more was likely to be clinically meaningful. Analysis of covariance was used to compare treatment endpoints at 4 weeks, adjusting for baseline observation, and using the last observation carried forward approach for missing values.

For constipation symptoms, mean BFI scores at randomisation were similarly high in the oxycodone plus naloxone and oxycodone alone groups (63.97 and 62.40 respectively). After 4 weeks, constipation symptoms were significantly more improved in the oxycodone plus naloxone group than among those receiving oxycodone alone (difference in change from baseline in BFI score=−11.14, 95% CI −19.03 to −3.24, p<0.01). Sensitivity analyses (using a mixed-effects model for repeated measures, adjusting for clinic visit and interaction between

treatment and clinic visit, and assuming a constant treatment effect over visits) also supported this result.

For chronic pain, mean scores on the Brief Pain Inventory–Short Form at baseline were similar in the oxycodone plus naloxone and oxycodone alone groups (4.16 and 4.18 respectively) and remained comparable after 4 weeks (3.50 and 3.52 respectively). Oxycodone plus naloxone was found to be non-inferior to oxycodone (least squares mean difference=0.011, p<0.01). Sensitivity analyses also supported this result. Rates of adverse drug reactions were comparable between those who did and did not receive naloxone (38.0% versus 34.8%), as were rates of serious adverse drug reactions (5.4% versus 3.3%).

Limitations of the evidence included the absence of a comparison with oral morphine plus optimal laxative therapy, which lessened the relevance of the study to NICE CG140.

Results from this trial suggest that sustained release oxycodone plus naloxone appears to improve symptoms of constipation compared with oxycodone alone (although not quite reaching a clinically meaningful difference as defined by the authors), while maintaining a similar analgesic effect.

A systematic review and meta-analysis by **Ford et al. (2013)** also examined pharmacological therapies for opioid-induced constipation in adults. RCTs of mu-opioid receptor antagonists (methylnaltrexone, naloxone[2], and alvimopan[3]), prucalopride[4] (or other 5-hydroxytryptamine receptor agonists/antagonists), lubiprostone[5], or linaclotide[2], were eligible. A total of 17 trials (n=5174) were identified, of which 14 assessed mu-opioid receptor antagonists (6 of methylnaltrexone, 4 of naloxone, 4 of alvimopan), 2 assessed lubiprostone (although data were only available in abstract form and could not be meta-analysed), and 1 prucalopride. All trials were placebo-controlled. Of the 17 included studies, only 2 were in patients with advanced illness (therefore of direct relevance to NICE CG140) – both of which examined methylnaltrexone versus placebo in patients who were laxative-refractory. The primary outcome of the review was efficacy in terms of failure to respond to therapy. Data were pooled using a random-effects model.

A meta-analysis of all trials of mu-opioid receptor antagonists showed a significant effect versus placebo for opioid-induced constipation (relative risk of failure to respond to therapy=0.69, 95% CI 0.63 to 0.75, p<0.00001; 14 trials, n=4101). A significantly reduced relative risk of failure to respond to therapy versus placebo was also observed in the 2 individual trials of methylnaltrexone in patients with advanced illness (0.61, 95% CI 0.40 to 0.91, n=134; and 0.47, 95% CI 0.34 to 0.64, n=154). A safety meta-analysis revealed a significantly greater risk of any adverse event with mu-opioid receptor antagonists than placebo (relative risk=1.11, 95% CI 1.04 to 1.20; 10 trials, n=2945). For individual adverse events, abdominal pain and diarrhoea were significantly more common with active therapy, but reversal of analgesia was not significantly different versus placebo.

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[2] At the time of publication of this Evidence Update, naloxone and linaclotide did not have UK marketing authorisation for opioid-induced constipation and are not recommended by NICE CG140 (Note: a combination product containing naloxone and oxycodone is licensed for severe pain that can be adequately managed only with opioid analgesics).

[3] At the time of publication of this Evidence Update, alvimopan did not have UK marketing authorisation and was not available in the UK.

[4] At the time of publication of this Evidence Update, prucalopride did not have UK marketing authorisation specifically for opioid-induced constipation and is not recommended by NICE CG140 for this indication (Note: NICE technology appraisal 211 recommends prucalopride as an option for the treatment of chronic constipation in women, though not specifically opioid-induced constipation).

[5] At the time of publication of this Evidence Update, lubiprostone did not have UK marketing authorisation for opioid-induced constipation and is not recommended by NICE CG140.

Limitations of the evidence included that:

- Most studies were not in a palliative care setting, and all trials used a placebo comparator rather than optimised laxative therapy.
- The authors stated that only half of the studies were at low risk of bias, and that there was significant heterogeneity between studies. Funnel plot asymmetry suggesting potential publication bias was also noted.
- Most trials were of secondary or tertiary care, so results may not be generalisable to primary care.

Taken together, these studies suggest that mu-opioid receptor antagonists appear to be safe and effective treatments for opioid-induced constipation. However, evidence of the efficacy of these drugs in a palliative care setting, particularly when compared with optimised laxative therapy, is limited. This evidence is therefore unlikely to have an impact on current recommendations in NICE CG140 that laxative treatment should be prescribed for all patients initiating strong opioids.

Further research in palliative care settings, to compare mu-opioid receptor antagonists with optimised laxative therapy, particularly among patients on maintenance treatment with oral morphine, is needed.

Key references

Ahmedzai SH, Nauck F, Bar-Sela G et al. (2012) A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliative Medicine 26: 50–60

Ford AC, Brenner DM, Schoenfeld PS (2013) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. American Journal of Gastroenterology 108: 1566–74

1.8 Management of nausea

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.9 Management of drowsiness

No new key evidence for this section was selected for inclusion in this Evidence Update.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Starting strong opioids – titrating the dose

- Oral morphine for cancer pain.

First-line treatment if oral opioids are not suitable – transdermal patches

- Transdermal fentanyl for cancer pain.

First-line treatment for breakthrough pain in patients who can take oral opioids

- Opioids for the management of breakthrough pain in cancer patients.

Further evidence uncertainties for opioids in palliative care can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Opioids in palliative care. NICE clinical guideline 140 (2012)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 27 May 2011 (the end of the search period of NICE clinical guideline 140) to 27 November 2013:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO
- Web of Science

The Evidence Update search strategy replicates the strategy used by NICE CG140 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. Changes to the original search strategy included an additional line for further drug terms (line 16).

The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews.

Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

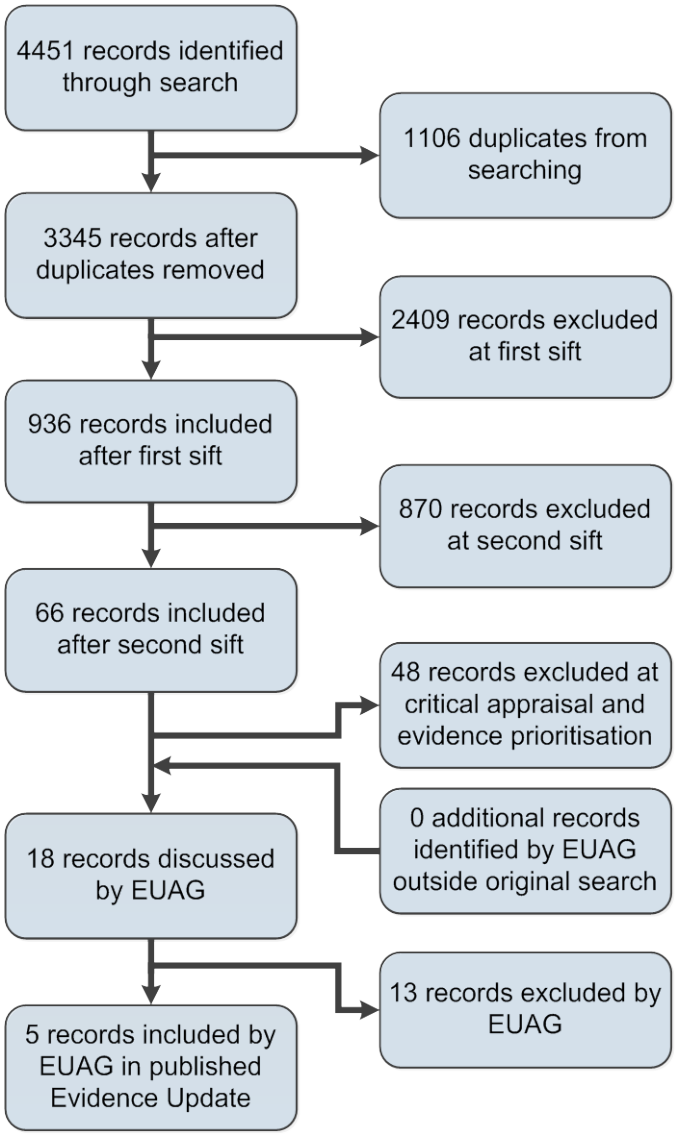
See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.

Table 1 MEDLINE search strategy (adapted for individual databases)

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$).tw.
16	(dextromoramide or OTFC or dextropropoxyphene or palfium or palface or sufenta* or nalbuphine or nubain or tramadol or zamadol or zydol or tapentadol or palexia).tw.
17	or/1-16
18	choice behavior/
19	decision making/
20	exp decision support techniques/
21	((patient$ or consumer$) adj3 (decision$ or choice or preference or participation)).tw.
22	((personal or interpersonal or individual) adj3 (decision$ or choice or preference$ or participat$)).tw.
23	(decision$ adj3 (aid$ or support$)).tw.
24	18 or 19 or 20 or 21 or 22 or 23
25	exp Patient Participation/
26	pamphlets/
27	exp Audiovisual Aids/
28	(video$1 or dvd$).tw.
29	exp Internet/
30	exp Self-Help Groups/
31	(support$ adj2 (group$ or meet$)).tw.
32	exp Patient Education/mt
33	((inform$ or support$) adj2 (tool$ or method$ or group$)).tw.
34	(information adj2 (need$ or support$)).tw.
35	(information adj2 (leaflet$ or booklet$ or pack$ or material$)).tw.
36	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37	((breakthrough or break through) adj3 pain).tw.
38	((spontaneous or severe or cancer* or intractable or refractory) adj3 pain).tw.
39	incident$ pain.tw.
40	((transitory or transient) adj pain).tw.
41	episodic pain.tw.
42	"breakthrough pain"/
43	37 or 38 or 39 or 40 or 41 or 42
44	Drug Administration Schedule/
45	Drug Monitoring/mt
46	Titrimetry/
47	(titrimetry or titrat$).tw.
48	(autotitrat$ or auto$ titrat$).tw.
49	(volumetry or volumetric analys?s).tw.
50	44 or 45 or 46 or 47 or 48 or 49
51	exp Chemistry, Pharmaceutical/
52	formulat$.tw.
53	((immediate or non-sustained) adj2 release).tw.
54	Delayed-Action Preparations/
55	((sustained or modified or slow or controlled or continuous or prolonged or extended) adj release).tw.
56	51 or 52 or 53 or 54 or 55

57	exp Administration, Oral/
58	exp Administration, Cutaneous/
59	exp Infusions, Subcutaneous/
60	(transdermal or trans-dermal or patch$ or cream$ or ointment$ or unguent$).tw.
61	((percutaneous or dermal or cutaneous or skin or topical$ or transcutaneous or trans-cutaneous) adj2 (administ$ or deliver$ or route$ or method$)).tw.
62	((oral$ or mouth) adj2 (administ$ or deliver$ or route$ or method$)).tw.
63	((subcutaneous$ or infusion$ or implant$ or hypoderm$ or parenteral$) adj2 (administ$ or deliver$ or route$ or method$)).tw.
64	57 or 58 or 59 or 60 or 61 or 62 or 63
65	exp Antiemetics/
66	(antiemetic$ or anti emetic$ or anti-emetic$ or anti-nause$ or anti nause$ or emetogen$).tw.
67	65 or 66
68	Lethargy/
69	(drows$ or sleepiness or sleepy or letharg$ or somnolen$ or sluggish or indolen$).tw.
70	68 or 69
71	exp Laxatives/
72	(laxative$ or laxation).tw.
73	purgative$.tw.
74	aperient$.tw.
75	cathartic$.tw.
76	(evacuative$ or evacuant$).tw.
77	costive$.tw.
78	(bulking agent$ or osmotic agent$ or enterokinetic agent$).tw.
79	((stool$ or faecal or fecal) adj soften$).tw.
80	70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79
81	43 or 50 or 56 or 64 or 67 or 70 or 80
82	(addresses or autobiography or bibliography or biography or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or historical article or in vitro or interactive tutorial or lectures or legal cases or legislation or letter or news or newspaper article or overall or periodical index or portraits).pt.
83	17 not 82
84	animal/ not human/
85	83 not 84
86	limit 85 to english language
87	limit 86 to ed=20110527-20131130
88	limit 87 to yr="2011 -Current"
89	36 and 88
90	81 and 88

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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