National Institute for Health and Care Excellence

4-year surveillance (2016) – Palliative care for adults: strong opioids for pain relief (2012) NICE guideline CG140

Appendix A: Summary of new evidence from surveillance

Communication

140 – 01 **What information do patients with advanced and progressive disease who require strong opioids, or their carers, need to:**

- **consent to opioid treatment, and**
- **monitor the effectiveness and side effects of the opioid?**

Recommendations derived from this question

1.1.1 When offering pain treatment with strong opioids to a patient with advanced and progressive disease, ask them about concerns such as:

- addiction
- tolerance
- side effects
- fears that treatment implies the final stages of life.

1.1.2 Provide verbal and written information on strong opioid treatment to patients and carers, including the following:

- when and why strong opioids are used to treat pain
- how effective they are likely to be
- taking strong opioids for background and breakthrough pain, addressing:
  - how, when and how often to take strong opioids
  - how long pain relief should last
- side effects and signs of toxicity
- safe storage
- follow-up and further prescribing
- information on who to contact out of hours, particularly during initiation of treatment.

1.1.3 Offer patients access to frequent review of pain control and side effects.

Surveillance decision

This review question should not be updated.

Communication skills training

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A randomised controlled trial (RCT)[1] (n=115) assessed training in communication skills compared with wait-list for oncology nurses working with people with cancer pain. Nurses were assessed using a recording of an interview with a patient with cancer who was reluctant to take morphine. Assessments were done at baseline and after training, or after 3 months in the wait-list group. All interviews were assessed by an investigator who was blind to treatment allocation and timing of the interview. After training, nurses asked more questions about cognitive representations associated with pain treatment, and the emotional component of pain. Additionally, decision-making interactions about pain management were less paternalistic.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggests that communication skills training for oncology nurses can improve interactions with patients who are considering starting strong opioids. This finding is broadly consistent with the recommendations about providing information to patients.

New evidence is unlikely to change guideline recommendations.

Side-effects of opioid treatment

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance review
The National Institute for Health Research commissioned a Cochrane review[2] to examine adverse effects, of 4 opioids in cancer pain studies as a close approximation to possible effects in people near the end of life. The review included 77 RCTs (n=5,619) of morphine, fentanyl, oxycodone, and codeine and looked at consciousness, appetite and thirst in particular. Proportions of each adverse event were calculated for each drug and for all drugs combined. The authors reported that most studies had potential bias and 60 studies included fewer than 50 participants. Additionally, the studies had major problems with reporting of adverse events. No direct measures of consciousness, appetite or thirst were identified. For opioids used to treat cancer pain, adverse event incidence rates were 25% for constipation, 23% for somnolence, 21% for nausea, 17% for dry mouth, and 13% for vomiting, anorexia, and dizziness. Asthenia, diarrhoea, insomnia, mood change, hallucinations and dehydration occurred at incidence rates of 5% and below.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggests that adverse events are frequent with strong opioids.

This finding is broadly consistent with the recommendations about providing information on side effects of opioid treatment to patients. It provides clinicians with evidence about the types of adverse events patients are most likely to encounter.

New evidence is unlikely to change guideline recommendations.

Starting strong opioids – titrating the dose

140 – 02 Are immediate-release opioids (morphine or oxycodone) more effective than sustained-release opioids (morphine or oxycodone) or transdermal patches (fentanyl or buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?

Recommendations derived from this question

1.1.4 When starting treatment with strong opioids, offer patients with advanced and progressive disease regular oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain.

1.1.5 For patients with no renal or hepatic comorbidities, offer a typical total daily starting dose schedule of 20–30 mg of oral morphine (for example, 10–15 mg oral sustained-release morphine twice daily), plus 5 mg oral immediate-release morphine for rescue doses during the titration phase.

1.1.6 Adjust the dose until a good balance exists between acceptable pain control and side effects. If this balance is not reached after a few dose adjustments, seek specialist advice. Offer patients frequent review, particularly in the titration phase.

1.1.7 Seek specialist advice before prescribing strong opioids for patients with moderate to severe renal or hepatic impairment.

Surveillance decision

This review question should not be updated.

Oral morphine

2-year Evidence Update

A Cochrane review[3] assessed 62 RCTs (n=4,241) of oral morphine compared with placebo or active control in cancer pain. Trials with fewer than 10 participants were excluded and 36 studies had a cross-over design.

Meta-analysis was not possible because of insufficient comparable data:

- 15 studies compared sustained-release oral morphine with immediate-release oral morphine.
- 14 studies compared dosing strategies for sustained-release morphine.
- 6 studies compared immediate-release morphine with other opioids.
- Several other studies involved comparing different dosing strategies, or different routes of administration, or compared opioids with non-opioid treatments.

Data were extracted for the number or proportion of participants with 'no worse than mild pain' or treatment success (very satisfied, or very good or excellent on patient global impression scales).

For studies reporting data on individual participants (17 studies, n=377), 96% of participants had 'no worse than mild pain'. Morphine was found to be effective with no difference in pain relief between immediate-release and sustained-release formulations, and both methods were amenable to dose-titration. Adverse effects were common and around 6% of participants stopped treatment because of intolerable adverse effects.

4-year surveillance summary

An RCT[4] (n=240) assessed low-dose morphine versus weak opioids in moderate cancer pain. Response was defined as a 20% reduction in pain intensity. Morphine was associated with significantly increased response rates from week 1. People in the weak opioid group more

frequently changed treatment because of inadequate analgesia.

Topic expert feedback
Topic experts highlighted the study comparing low-dose strong opioids and weak opioids. This paper was thought to indicate a need to consider starting strong opioids before pain becomes severe.

Impact statement
Oral morphine effectively manages cancer pain, and immediate-release and sustained-release morphine work equally well and can be titrated to the patient's needs. This evidence is consistent with recommendations in NICE guideline CG140 that patients starting treatment with strong opioids should be offered sustained-release or immediate-release oral morphine depending on preference.

New evidence suggests that low-dose opioids may be more effective in moderate cancer pain than weak opioids. However, this study is not entirely in the scope of the guideline because the comparator was weak opioids, and the guideline dealt only with use of strong opioids and does not cover making the decision to start strong opioids. The dose of morphine used in this study (30 mg daily) is comparable to the starting dose recommended in NICE guideline CG140, so in this respect the new evidence is consistent with current guidance.

New evidence is unlikely to change guideline recommendations.

Oxycodone

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[5] assessed 17 RCTs (n=1,390) of oxycodone compared with placebo or active control in cancer pain. In pooled analysis of 3 studies of sustained-release oxycodone compared with immediate-release oxycodone the effects on pain were similar. Additionally, none of the included studies reported differences in pain intensity between treatment groups. In 3 of 4 studies of sustained-release oxycodone compared with immediate-release oxycodone, treatment acceptability and adverse events were similar, and 1 study suggested fewer adverse events with sustained-release oxycodone. In pooled analysis of 5 studies of sustained-release oxycodone compared with sustained-release morphine there was no difference in pain intensity scores, adverse events, treatment acceptability, or quality of life. In 7 studies comparing various oxycodone formulations or comparing oxycodone with other opioids, none found any clear superiority or inferiority of oxycodone for cancer pain; neither as an analgesic agent nor in terms of adverse event rates and treatment acceptability. The authors noted that the evidence base was limited by small sample sizes and high loss to follow up.

Topic expert feedback
Topic experts indicated that non-proprietary oxycodone is now available. However, it is still substantially more expensive than oral morphine.

Impact statement
The new evidence suggests that there is no difference in efficacy between immediate-release and sustained-release formulations of oxycodone, which is in line with similar findings for morphine considered in developing NICE guideline CG140. However, this study provides no evidence to suggest that oxycodone should be considered as first-line treatment instead of morphine.

New evidence is unlikely to change guideline recommendations.

Morphine versus oxycodone

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An RCT[6] (n=198) assessed oral morphine compared with oral oxycodone in people with cancer pain. Doses were titrated to adequate pain control, and the patient could switch to the other opioid if they had inadequate analgesia or

unacceptable adverse effects. The proportion of people classed as responding was reported to not differ significantly between groups. Switching to the other opioid was associated with no significant difference in subsequent response between groups; however, the number of people switching was low. Adverse reactions did not differ between morphine and oxycodone.

Topic expert feedback
Topic experts indicated that non-proprietary oxycodone is now available. However, it is still substantially more expensive than oral morphine.

Impact statement
The new evidence suggested that there is no benefit of oxycodone over morphine in people with cancer pain which is the recommended first-line treatment.

New evidence is unlikely to change guideline recommendations.

Oxycodone in Parkinson's disease

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A phase II RCT[7] (n=202) assessed sustained-release oxycodone plus naloxone or placebo in people with stage II–IV Parkinson's disease and chronic, severe pain (score of 6 on an 11 point scale). In per-protocol analysis (n=194) there was no significant difference from baseline in pain scores at 16 weeks between oxycodone plus naloxone or placebo. Nausea and constipation were more common in the oxycodone plus naloxone group.

Another report[8] from this trial showed that oxycodone plus naloxone was associated with small statistically significant reductions in pain compared with placebo at weeks 4, 8 and 12, but not at week 16. The reductions in pain may not have been clinically significant.

In a third report[9] Clinical Global Impression-Improvement and Patient Global Impression-Improvement were significantly improved by week 16. Overall adverse events and treatment-related adverse events appeared to be similar between groups.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggested that oxycodone plus naloxone may not be clinically useful in people with Parkinson's disease and chronic pain. No evidence was identified for other treatments for pain in Parkinson's disease. NICE CG140 has no recommendations about treating pain in Parkinson's disease. This new evidence is unlikely to inform recommendations in this area. The guideline on Parkinson's disease (NICE guideline CG35) has general recommendations about palliative care, but does not cover managing pain.

New evidence is unlikely to change guideline recommendations.

Buprenorphine

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[10] assessed 19 RCTs (n=1,421) of buprenorphine compared with placebo or active control in cancer pain. The authors reported that meta-analysis was not possible, so results were summarised narratively. Of 11 studies comparing buprenorphine to another drug assessing patient preference or side effects, buprenorphine was better than the comparator in 5 studies, no different in 3 studies and worse than comparator in 3 studies. Pain intensity ratings did not differ significantly between intramuscular and suppository formulations of buprenorphine. In 1 study, dizziness, nausea, vomiting and overall adverse events were significantly higher with intramuscular buprenorphine compared with suppository. In 1 study, sublingual buprenorphine was associated with faster onset of pain relief compared with subcutaneous buprenorphine, with similar duration of analgesia and no significant differences in adverse events. Transdermal buprenorphine was superior to

placebo in 2 studies, but another study found no difference between transdermal buprenorphine and placebo. The studies that examined different doses of transdermal buprenorphine did not report a clear dose-response relationship. The authors noted that evidence for all outcomes was very low quality.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new evidence suggests that buprenorphine may be effective for pain relief; however there is no clear evidence that it is better than oral morphine, which is the recommended first-line treatment.

New evidence is unlikely to change guideline recommendations.

Additional studies

4-year surveillance summary
A further 2 RCTs[11,12] were identified but were not thought to impact on current recommendations. One of these studies[11] assessed efficacy and adherence of immediate versus sustained-release morphine. The other[12] assessed switching versus combination of opioids in uncontrolled cancer pain; however the abstract did not specify which opioids were used in the study.

First-line maintenance treatment

140 – 03 Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl or buprenorphine) as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids?

Recommendations derived from this question

1.1.8 Offer oral sustained-release morphine as first-line maintenance treatment to patients with advanced and progressive disease who require strong opioids.

1.1.9 Do not routinely offer transdermal patch formulations as first-line maintenance treatment to patients in whom oral opioids are suitable.

1.1.10 If pain remains inadequately controlled despite optimising first-line maintenance treatment, review analgesic strategy and consider seeking specialist advice.

Surveillance decision

This review question should not be updated.

Tapentadol

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
Two reports from an RCT[13,14] (n=504) assessed sustained-release tapentadol compared with sustained-release morphine in people with moderate to severe cancer pain (defined as pain intensity score greater than 5). Participants were randomly allocated in a 2:1 ratio to sustained-release tapentadol (100–250 mg twice daily) compared with sustained-release morphine (40–100 mg twice daily). Both drugs were titrated to optimum dosages over 2 weeks. Immediate-release morphine 10 mg was used for breakthrough pain (rescue). Tapentadol was associated with a

numerically lower rate of response than morphine. However, the reported per-protocol analysis suggested that tapentadol met the prespecified non-inferiority criterion of less than 20% difference in response rates between groups. Fewer gastrointestinal adverse events were reported in the group on tapentadol compared with morphine, but the abstract did not report statistical analysis.

After the titration phase, participants (n=327) with pain intensity score less than 5 and taking up to 2 rescue doses in the last 3 days underwent a second random allocation. Participants who took sustained-release morphine in the first phase continued with that treatment. People who took tapentadol in the first phase were randomly allocated to continue tapentadol or to placebo. In the second phase, response was defined as the average pain intensity score less than 5 and rescue doses seen in the last 3 days of the first phase. In the second phase, significantly more people in the tapentadol group had treatment response than in the placebo group. However, the placebo response was notably high at almost 50%. Adverse events in the tapentadol and morphine groups did not differ from each other, but were both somewhat higher than in the placebo group.

A Cochrane review[15] assessed 4 RCTs (n=1,029) of tapentadol in cancer pain. Studies with fewer than 10 participants per group were excluded. All included studies had a dose-titration phase then a maintenance phase. Tapentadol was taken twice daily at doses of 50–500 mg per day. Immediate-release morphine or oxycodone was available to participants in all studies as rescue treatment. Overall, 440 people participated in classically designed RCTs, and 589 people participated in enriched-enrolment, randomised-withdrawal trials; 338 participants took tapentadol throughout the maintenance phase of their trial. The authors noted that all studies were at risk of overestimating efficacy. Data were insufficient for meta-analysis. Response rates for pain intensity were comparable across treatment groups in each study. Treatment emergent adverse event rates were high (50–90%), most commonly nausea, vomiting and constipation, with no difference in serious adverse events between tapentadol, morphine or oxycodone.

A non-inferiority RCT[16] (n=343) conducted in Japan and Korea assessed 4 weeks of sustained-release tapentadol (25–200 mg twice daily) compared with sustained-release oxycodone (5–40 mg twice daily) in moderate to severe cancer pain. Sustained-release tapentadol met the predefined threshold for non-inferiority and was associated with fewer gastrointestinal adverse events than sustained-release oxycodone, but statistical analysis of this finding was not reported in the abstract.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence suggests that tapentadol may be effective in cancer pain; however, it shows no evidence of benefit over oral morphine, which is the recommended first-line maintenance treatment.

Tapentadol is licensed in the UK for severe pain only.

New evidence is unlikely to change guideline recommendations.

Hydromorphone versus oxycodone

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An RCT[17] (n=260) in China assessed non-inferiority of once-daily sustained-release hydromorphone (8–32 mg) compared with twice-daily sustained-release oxycodone (10–40 mg) in people with moderate to severe cancer pain. An 8-day dose titration phase was followed by a 28-day maintenance phase. Per-protocol analysis of 81 people who completed the maintenance phase suggested that hydromorphone was non-inferior to oxycodone based on the prespecified margin of −1.5% difference between groups in ratings of worst pain in the past 24 hours on the brief pain inventory. Adverse events were reported to be comparable between groups but statistical analysis was not reported.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence suggests that hydromorphone may be effective in cancer pain; however, it shows no evidence of benefit over oral morphine, which is the recommended first-line maintenance treatment.

Hydromorphone is licensed in the UK for severe pain only.

New evidence is unlikely to change guideline recommendations.

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

140 – 04 Are 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 for whom oral treatment is not suitable?

Recommendations derived from this question

1.1.11 Consider initiating transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed.

1.1.12 Use caution when calculating opioid equivalence for transdermal patches:

- A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily.
- A transdermal buprenorphine 20 microgram patch equates to approximately 30 mg oral morphine daily.

Surveillance decision

This review question should not be updated.

An editorial and factual correction is needed to replace recommendation 1.1.12 with a cross-reference to the more recent guidance in 'Controlled drugs: safe use and management (NICE guideline NG46)'.

Transdermal fentanyl for cancer pain

2-year Evidence Update
A Cochrane review[18] assessed 9 RCTs (n=1,382) of transdermal fentanyl compared with placebo or active control in cancer pain. Studies with fewer than 10 participants were excluded. One study was published in Turkish and was not translated. One trial was described as an 'enriched enrolment randomised withdrawal trial'. Participants received transdermal fentanyl, various morphine formulations, methadone, or codeine plus paracetamol.

Data were extracted for the number or proportion of participants with 'no worse than mild pain' or treatment success (very satisfied, or very good or excellent on patient global impression scales). The authors noted that there were 'major sources of potential bias' and they could not meaningfully analyse adverse events such as nausea, abdominal pain, gastrointestinal bleeding, and confusion. Meta-analysis was not possible because of insufficient comparable data.

In 7 studies reporting results after about 2 weeks, most participants had no worse than mild pain. Fewer participants experienced constipation with transdermal fentanyl than with oral morphine; the number needed to treat to prevent constipation was 5.5.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
Topic expert feedback suggested that the recommendation on opioid equivalence was no longer relevant because more recent NICE guidance on safely using controlled drugs covers this issue.

Impact statement
The new evidence suggests that most patients with moderate to severe cancer pain receiving transdermal fentanyl have no worse than mild pain and experience less constipation compared with oral morphine. The evidence is consistent with the recommendation in NICE guideline CG140 that transdermal patches (such as fentanyl) should be considered for patients in whom oral opioids are not suitable.

New evidence is unlikely to change guideline recommendations.

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

140 – 05 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 for whom oral treatment is not suitable?

Recommendations derived from this question

1.1.13 Consider initiating subcutaneous opioids with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are unstable, supported by specialist advice where needed.

Surveillance decision

No new information was identified at any surveillance review.

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140 – 06 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 for whom oral opioids are not suitable?

Recommendations derived from this question

The full guideline noted that recommendation 1.1.11 (see question 140-04 above) covered the necessary actions from reviewing this question. The guideline committee did not make any additional recommendations.

Surveillance decision

No new information was identified at any surveillance review.

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

140 – 07 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)?

Recommendations derived from this question

1.1.14 Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.

1.1.15 Do not offer fast-acting fentanyl as first-line rescue medication.

1.1.16 If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

Surveillance decision

This review question should not be updated.

Fentanyl

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An RCT[19] assessed fentanyl buccal tablet compared with oral morphine in people with cancer taking more than 60 mg of morphine (or equivalent opioid) and more than 3 episodes of breakthrough pain per day. Overall, 263 episodes of breakthrough pain were treated in the study. Fentanyl buccal tablet was associated with greater pain relief at 15 minutes and at 30 minutes compared with control.

Additional studies

A further 5 RCTs[20-24] of oral transmucosal and intranasal fentanyl were identified but were thought not to have a substantial effect on the evidence base.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence suggests that buccal fentanyl may work quicker than oral morphine or oxycodone. This finding is consistent with evidence reviewed in developing the guideline, which also found that fentanyl buccal tablets worked faster than oral morphine. In making the recommendations, the guideline committee considered the costs of fentanyl buccal tablets against the cost of oral morphine. 'It felt the cost impact of recommending fentanyl over immediate-release morphine or oxycodone would be considerable and therefore could not be justified.' The cost of fentanyl buccal tablets has not reduced substantially since this recommendation was made.

New evidence is unlikely to change guideline recommendations.

Management of constipation

140 – 08 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?

Recommendations derived from this question

1.1.17 Inform patients that constipation affects nearly all patients receiving strong opioid treatment.

1.1.18 Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids.

1.1.19 Inform patients that treatment for constipation takes time to work and adherence is important.

1.1.20 Optimise laxative treatment for managing constipation before considering switching strong opioids.

Surveillance decision

This review question should not be updated.

Lubiprostone

Studies relating to lubiprostone have not been summarised. Lubiprostone was considered for a NICE technology appraisal but it was suspended in 2014 because the manufacturer did not have marketing authorisation for use in opioid-induced constipation. NICE has produced the technology appraisal guidance 'Lubiprostone for treating chronic idiopathic constipation' (TA318).

The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An RCT[29] relating to lubiprostone was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The NICE technology appraisals team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.

Naloxegol

Studies relating to 'Naloxegol for treating opioid-induced constipation' (TA345) have not been summarised. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
4 RCTs[25-28] relating to naloxegol were identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The NICE technology appraisals team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.

Methylnaltrexone

Studies relating to 'Methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care' (March 2013) TA277 have not been summarised. Guidance on methylnaltrexone bromide in opioid-induced constipation is currently being developed. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
An RCT[30] relating to methylnaltrexone was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The NICE technology appraisals team has been informed about all new evidence.

New evidence is unlikely to change guideline recommendations.

General laxatives

2-year Evidence Update
No relevant evidence was identified.

4-year surveillance summary
A Cochrane review[31] assessed 5 studies of laxatives (lactulose, senna, co-danthramer, misrakasneham, docusate and magnesium hydroxide with liquid paraffin) for constipation in people receiving palliative care. It was not possible to do meta-analysis because the studies compared different laxatives or combinations of laxatives. There was no evidence on whether individual laxatives were more effective than others or caused fewer adverse effects. None of the studies evaluated polyethylene glycol or any intervention given rectally. The authors concluded that trials of laxatives in palliative care are needed.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
This study shows no clear evidence to guide choice of laxative, therefore the recommendations to prescribe laxatives at effective doses and encourage adherence remain relevant.

Misrakasneham is not available in the UK.

New evidence is unlikely to change guideline recommendations.

Naloxone

2-year Evidence Update
An RCT[32] (n=185) assessed naloxone plus oxycodone versus oxycodone alone in people with moderate or severe cancer pain. Any laxatives were stopped before the trial started and then sustained-release oxycodone (with or without naloxone) was titrated to a maximum of 120 mg/day, with immediate-release oxycodone available for breakthrough pain. Bisacodyl was used as rescue laxative.

Oxycodone plus naloxone was non-inferior to oxycodone alone for chronic pain. Constipation scores reduced to a significantly greater degree with naloxone than without naloxone, but did not meet the trial's predefined target for clinical significance. Rates of adverse drug reactions and serious adverse drug reactions were comparable between groups.

4-year surveillance summary
A cost-utility analysis[33] from an NHS perspective assessed a sustained-release combination tablet of oxycodone plus naloxone compared with sustained-release oxycodone. The model was constructed with data from RCTs in people with moderate to severe pain from cancer or from non-cancer causes who had opioid-induced constipation despite use of

2 laxatives (n=178). The incremental cost-effectiveness ratio (ICER) was £7,822 for sustained-release oxycodone plus naloxone compared with sustained-release oxycodone.

A phase II RCT[34] (n=40) assessed sustained-release naloxone compared with placebo to treat opioid-induced constipation in non-cancer pain. Each of 4 doses (2.5 mg, 5 mg, 10 mg, and 20 mg) was assessed in 10 patients, given once-daily for 3 weeks and then twice daily for 4 weeks.

Spontaneous bowel movements were significantly increased with doses of 5 mg daily and above compared with baseline. There was no significant difference in measures of opioid withdrawal or pain relief. Adverse events were more frequent in the placebo group.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
These studies suggest that naloxone may be safe and effective for reducing opioid-induced constipation. However, no trials compared adding naloxone to oxycodone with oxycodone plus optimised laxative therapy – although a cost-effectiveness analysis suggested that naloxone was cost-effective in people with opioid-induced constipation despite using 2 laxatives.

However, it is unclear how cost-effective oxycodone plus naloxone would be compared with recommended first-line therapy with morphine plus optimised laxative therapy. Overall, this evidence is unlikely to have an impact on current recommendations in NICE guideline CG140 that laxative treatment should be prescribed for all patients initiating strong opioids.

Oral naloxone is not available in the UK as a stand-alone preparation (only in combination with oxycodone).

New evidence is unlikely to change guideline recommendations.

Mu-opioid receptor antagonist drug class analysis

2-year Evidence Update
A systematic review and meta-analysis[35] assessed 14 RCTs (n=4,101) of mu-opioid receptor antagonists compared with placebo for opioid-induced constipation. Meta-analysis including all drugs from included studies (methylnaltrexone, naloxone, and alvimopan) suggested improvements in constipation compared with placebo. Meta-analyses for each individual drug showed similar results. Individual adverse events, abdominal pain and diarrhoea were significantly more common with active therapy, but reversal of analgesia was not significantly different versus placebo.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
These studies suggest that mu-opioid receptor antagonists may be safe and effective treatments for opioid-induced constipation. However, evidence of the efficacy of these drugs in palliative care, particularly when compared with optimised laxative therapy, was 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.

Alvimopan is not available in the UK.

New evidence is unlikely to change guideline recommendations.

Management of nausea

140 – 09 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?

Recommendations derived from this question

1.1.21 Advise patients that nausea may occur when starting strong opioid treatment or at dose increase, but that it is likely to be transient.

1.1.22 If nausea persists, prescribe and optimise anti-emetic treatment before considering switching strong opioids.

Surveillance decision

No new information was identified at any surveillance review.

Management of drowsiness

140 – 10 Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease who are taking strong opioids and experience drowsiness as a side effect?

Recommendations derived from this question

1.1.23 Advise patients that mild drowsiness or impaired concentration may occur when starting strong opioid treatment or at dose increase, but that it is often transient. Warn patients that impaired concentration may affect their ability to drive and undertake other manual tasks.

1.1.24 In patients with either persistent or moderate-to-severe central nervous system side effects:

- consider dose reduction if pain is controlled **or**
- consider switching opioids if pain is not controlled.

1.1.25 If side effects remain uncontrolled despite optimising treatment, consider seeking specialist advice.

Surveillance decision

No new information was identified at any surveillance review.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 **What are the most clinically effective and cost-effective methods of addressing patient and carer concerns about strong opioids, including anticipating and managing adverse effects, and engaging patients in prescribing decisions?**

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations. The new evidence measured the types of adverse effects that people may experience on strong opioids.

Ongoing research relevant to the research recommendation was found. An ongoing pilot study, Self-Management of Analgesia and Related Treatments at the End of life (SMARTE), was identified that is working towards addressing this research recommendation. However, an aim of the pilot study was to assess the feasibility of obtaining outcome data for a larger trial. The pilot study is expected to publish results in March 2017, and a subsequent trial is likely to take years more to be designed, conducted and have results published.

Surveillance decision

The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 02 **Is prophylactic prescription of anti-emetic treatment or the availability of anti-emetic treatment at the patient's home more effective in reducing nausea than the availability of prescription on request for patients starting strong opioids for the treatment of pain in advanced or progressive disease? The outcomes of interest are nausea, time to control of nausea, patient acceptability of treatment, concordance and use of healthcare resources.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 03 **Is early switching of opioid, on development of side effects, more effective at reducing central side effects than persisting with current opioid and dose reduction in patients starting strong opioids? The outcomes of interest are time to clinically effective pain control with acceptable side effects.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

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