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

NICE clinical guideline

Final draft, March 2012

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

Contents

Appendices C, D, E and F are in separate files.

Introduction

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

Despite the increased availability of strong opioids, published evidence suggests that pain which results from advanced disease, especially cancer, remains under-treated.

Each year 300,000 people are diagnosed with cancer in the UK and it is estimated that there are 900,000 people living with heart failure. Others live with chronic illness such as kidney, liver and respiratory disease, and with neurodegenerative conditions. Many people with these conditions will develop pain for which a strong opioid may be needed.

The 2008 World Cancer Declaration included a target to make effective pain control more accessible. Several key documents highlight the importance of effective pain control, including 'Improving supportive and palliative care for adults with cancer' (NICE cancer service guidance 2004), 'Control of pain in adults with cancer' (Scottish Intercollegiate Guidelines Network guideline 106), 'A strategic direction for palliative care services in Wales' (Welsh Assembly Government 2005) and 'End of life care strategy' (Department of Health 2008).

Strong opioids, especially morphine, are the principal treatments for pain related to advanced and progressive disease, and their use has increased significantly in the primary care setting. However, the pharmacokinetics of the various opioids are very different and there are marked differences in bioavailability, metabolism and response among patients. A suitable opioid must be selected for each patient and, because drug doses cannot be estimated or calculated in advance, the dose must be individually titrated. Effective and safe titration of opioids has a major impact on patient comfort.

The World Health Organization has produced a pain ladder[1] for the relief of cancer pain; strong opioids are represented on the third level of the three-step ladder.

The guideline will address first-line treatment with strong opioids for patients who have been assessed as requiring pain relief at the third level of the WHO pain ladder. It will not cover second-line treatment with strong opioids where a change in strong opioid treatment is required because of inadequate pain control or significant toxicity.

A number of strong opioids are licensed in the UK. However for pain relief in palliative care a relatively small number is commonly used. This guideline has therefore looked at the following drugs: buprenorphine, diamorphine, fentanyl, morphine and oxycodone. Misinterpretations and misunderstanding have surrounded the use of strong opioids for decades (see section 3.1), and these are only slowly being resolved. Until recently, prescribing advice has been varied and sometimes conflicting. These factors, along with the wide range of formulations and preparations, have resulted in errors causing underdosing and avoidable pain, or overdosing and distressing adverse effects. Despite repeated warnings from regulatory agencies, these problems have led on occasion to patient deaths, and resulted in doctors facing the General Medical Council or court proceedings. Additional guidance, including advice on reducing dosing errors with opioid medicines, patient safety incidents arising from medication errors involving opioids and safer use of injectable medicines is available from the National Patient Safety Agency[2] (NPSA).

This guideline will clarify the clinical pathway and help to improve pain management and patient safety. This guideline will not cover care during the last days of life (for example, while on the Liverpool Care Pathway).

Drug recommendations

Prescribers should refer to the 'British national formulary' for information about drug dosage. The guideline also assumes that prescribers will use a drug's

[1]The World Health Organization's pain ladder is available from http://www.who.int/cancer/palliative/painladder/en/
[2] The National Patient Safety Agency: http://www.npsa.nhs.uk/

summary of product characteristics to inform decisions made with individual patients.

Who this guideline is for

The target audience is non-specialist healthcare professionals initiating strong opioids for pain in adults with advanced and progressive disease. However, the guideline is likely to be of relevance to palliative care specialists as well.

Patient-centred care

This guideline offers best practice advice on the care of people with advanced and progressive disease, who require strong opioids for pain control. These patients are defined as those in severe pain who may be opioid-naive, or those whose pain has been inadequately controlled on step two of the WHO pain ladder.

Treatment and care should take into account patients' needs and preferences. People with advanced and progressive disease, who require strong opioids for pain control, should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Recommendations

Communication

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.

Starting strong opioids – titrating the dose

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, **with**
- 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.

First-line maintenance treatment

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.

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

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

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

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.

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

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.

Management of constipation

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.

Management of nausea

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.

Management of drowsiness

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[3] and undertake other manual tasks.

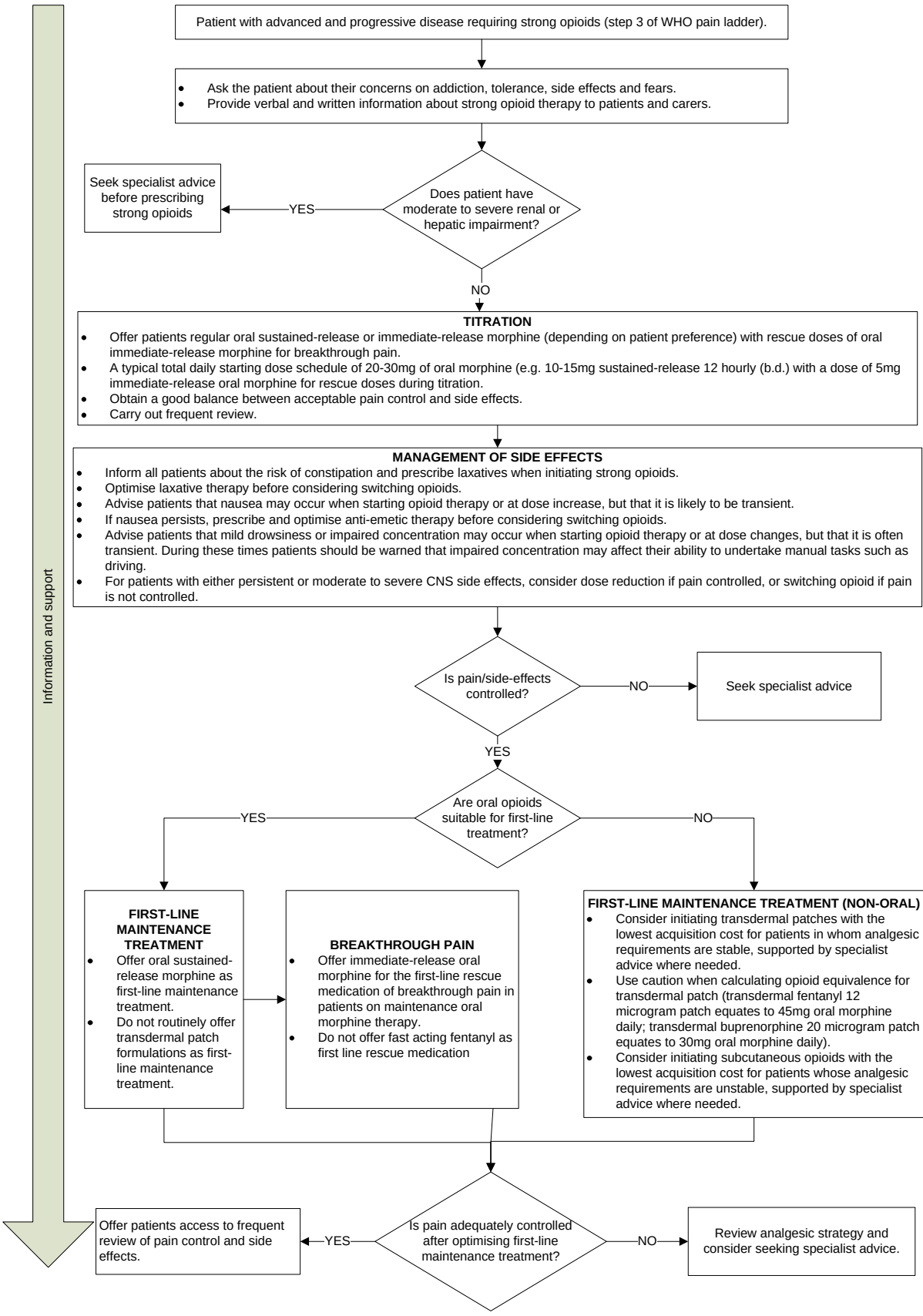
1.1.24 In patients with either persistent or moderate-to-severe central nervous system side effects:

- 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.

[3] http://www.dft.gov.uk/dvla/medical/ataglance.aspx

2 Care pathway



3 Evidence review and recommendations

For details of how this guideline was developed see appendix D.

3.1 Communication

Opioids are powerful medicines for pain relief and are given when weaker medications fail to provide pain relief. Several barriers to successful opioid treatment of pain have been identified. These include fear of addiction to opioids, worry about the potential for developing tolerance to treatment, concerns about side effects, reluctance to focus on pain relief rather than treating disease, fear of analgesic treatment masking symptoms of disease progression and the significance of starting opioid treatment in relation to the severity of illness. When barriers to treatment are identified and addressed, patients are more likely to take analgesia as prescribed. This may improve pain control and lessen adverse effects.

Good practice in prescribing any medicine needs an informed discussion about the potential benefits and harms of treatment before starting treatment. Ongoing monitoring of treatment should address patients' experiences and concerns about efficacy and side effects and should include discussion about how treatment might improve or impair quality of life.

3.1.1 Review question

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?

3.1.2 Evidence review

This review question focused on the information that patients and carers have found to be useful or not useful, or wanted or not wanted, when considering consenting to opioid treatment and when undergoing treatment with strong opioids. Papers were included if they contained any such information reported by patients or carers. For the review protocol, inclusion/exclusion criteria, and

a full list of excluded papers see appendix D. Three qualitative studies (Bender et al. 2008; Blanchard and Batten 1996; Reid et al. 2008) were identified for inclusion. All three studies examined aspects of cancer patients' information needs pertaining to pain and strong opioids. However, none of the main aims of the studies correspond to the main aims of this clinical question, and consequently the data provided by these studies are very limited. No evidence on carer information needs was identified. Table 1 lists the main characteristics of each of the included studies. GRADE was not used for this topic as it is not applicable for qualitative studies. All studies were appraised according to the NICE technical manual (2009), (see appendix E for full evidence tables).

Bender et al. (2008) conducted semi-structured interviews of 18 patients with breast cancer on what these patients wanted to know about pain. These patients wanted to know about all available options for pain control and how these drugs and treatments work, as well as about their expected side effects, and about the circumstances in which they are used to treat pain. Furthermore, the patients expressed a wish to know about the use and administration of analgesic medication, including when and how the medication should be taken, how often, for how long, when to expect pain relief, and the expected duration of the relief. Concerns about addiction and tolerance were common, particularly with respect to the use of opioids. Fear of unpleasant or unmanageable side effects prompted many to avoid or discontinue pain medication.

Blanchard and Batten (1996) interviewed 47 patients with terminal cancer, 31 of whom were either currently taking or had previously taken morphine. For 17 of the 31 patients taking or having previously taken morphine who contributed responses to the relevant (in this context) question, the most common questions or concerns related to addiction, side effects, whether opioid treatment means that end of life is near, and alcohol consumption while receiving opioid treatment. For 7 out of the 16 patients not on morphine who responded to the relevant (in this context) question, the main questions or concerns about potential morphine treatment also related to whether opioid

treatment signals that end of life is near, whether morphine is a poison, and the likely side effects.

Reid et al. (2008) interviewed 18 patients with cancer who had been approached to take part in a pain management trial. These interviews showed that the patients preferred unhurried consultations in which pain was seen as important, although some of the patients did not expect their pain to be addressed during oncology clinics because of the perception that the staff already had high workloads. The interviews also showed that the manner in which the professionals communicated about opioids was important. Participants felt more able to accept inclusion in the pain management trial when they were told that opioids were being started at a 'low dose' and opioids could be discontinued if side effects developed. The patients also appreciated professionals who spoke about opioids with knowledge and confidence but were sometimes suspicious about the idea of 'choice' ('They actually don't say, "Mr Smith, would you like to take the morphine?" They always say, "it's your choice". If it is my choice, what are they not telling me?'). Half of the participants mentioned trust in the professional as an important factor in their decision to take opioids. For some of the patients, trusting the professional meant that it allowed them to make their own decision, whereas for others, trust meant that they could allow the professional to make the decision on their behalf.

Table 1 Summary of included studies for information needs of patients with advanced and progressive disease who require strong opioids for pain, or their carers

Author (year)	Study design	Population (N, inclusion criteria)	Aim and method
Bender et al. (2008)	Qualitative study	N = 18 patients with pain from breast cancer or its treatment, ≥ 18 years old, and who were able to understand spoken and written English	Semi-structured interviews examining what the patients wanted to know about pain
Blanchard and Batten (1996)	Qualitative study	N = 47 patients with terminal cancer	Interviews examining cancer patients' knowledge of morphine
Reid et al. (2008)	Qualitative study	N = 18 patients recruited from a pain management trial that took place in a UK oncology centre. All patients who both entered and declined participation in the trial were approached to request an interview	Interviews examining the factors influencing the decision to accept or reject morphine when first offered to patients with cancer

See appendix E for the evidence tables in full.

3.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

3.1.3.1 Patients worry about addiction, tolerance and side effects and that opioid treatment signals that the end of life is near (three studies; VERY LOW QUALITY).

3.1.4 Health economic modelling

This topic did not lend itself to health economic evaluation because there is no comparative analysis of cost and outcomes.

The cost difference between different interventions (different information for the patient) is likely to be minimum, so this question is considered to be of low priority for economic analysis. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.1.5 Evidence to recommendations

The aim of this topic was to determine what information patients and carers need to consent to opioid treatment and monitor the effectiveness and side effects of opioid treatment.

The primary outcome of interest was the information needs reported by patients and carers both when considering treatment and when undergoing treatment with strong opioids. No evidence was found on carers' information needs.

Evidence was found relating to patients' information needs but this was limited and of very low quality. The GDG noted that the main aims of the studies appraised did not correspond with the main aims of this clinical question. They also noted that one of the studies was from 1996 and may therefore not reflect current practice. It was also unclear if these qualitative studies had reached data saturation. Despite these limitations, the GDG agreed that the data provided by these studies would still be helpful in forming recommendations.

The available evidence reported patient concerns about the use of opioids. The GDG considered that this was an important outcome because patient concerns can have a significant impact on whether or not a patient actually takes the opioid that has been prescribed. It therefore agreed that a recommendation should be made to explore patients' concerns when offering treatment with strong opioids.

The GDG noted that the evidence supported providing information to patients and carers and therefore agreed to recommend that patients and carers should be offered information on opioid treatment. However, the GDG also noted that there was variation between studies on what information was required and the format and method in which it was provided.

The GDG felt it was important that the recommendation specified what information should be offered to patients and carers because this can be a time of great anxiety and so extra effort needs to be made to address information needs. Therefore, based on its clinical experience, the GDG recommended a minimum level of information that should be offered. The

GDG was aware that by providing this level of detailed information there was a risk that patient anxiety could increase, causing them not to take the opioid. However, the GDG felt that the recommendation to explore patients' concerns would counteract this risk.

No formal cost-effectiveness analysis was conducted for this question. The GDG considered that the recommendations it had made constituted a good standard baseline of care but it was unsure of the economic implications of making these recommendations. It therefore recommended further research to investigate this.

The GDG felt that patients often have concerns about taking opioids but that provision of support is currently variable. The GDG agreed, based on its clinical experience, that it is good clinical practice to support patients during opioid treatment by frequently reviewing pain control and side effects and providing information on who to contact out of hours.

3.1.6 Recommendations and research recommendations for communication

Recommendation 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.

Recommendation 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.

Recommendation 1.1.3

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

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B1

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?

3.2 Introduction to first-line treatment

Morphine given orally is the oldest known opioid for treating moderate to severe pain associated with advanced and progressive disease. It is advocated in several international guidelines as a first-line strong opioid in this context (WHO pain ladder (1986); 'Morphine in cancer pain: modes of administration' (EAPC 1996, 2001); 'Control of pain in adults with cancer' (SIGN 2008). In recent years, the range of strong opioids available for clinical use, and their route of delivery, has broadened considerably. This range now includes additional oral preparations, transdermal patches, subcutaneous injections and rapidly acting transmucosal preparations.

Despite the increased availability of strong opioids, published evidence suggests that pain which results from advanced disease, especially cancer, remains under-treated. The explanation for this is complex and includes failure to assess pain and monitor symptoms; patients' and professionals' fears of opioids and their adverse effects; and difficulties accessing prescriptions and analgesia. Furthermore, the increased range of treatments may confuse some prescribers and so there is a clear need to identify the evidence base in support of strong opioids and produce guidance on their use. For the purpose of this short clinical guideline, only the following drugs commonly used in palliative care were considered: buprenorphine, diamorphine, fentanyl, morphine and oxycodone. Oral, transdermal and subcutaneous routes of administration were considered because these are

the commonly used methods of administration in people requiring palliative care. Intravenous and intramuscular administration were not included.

The GDG examined three contexts in which guidance would be beneficial regarding first-line opioid use for patients with advanced and progressive disease. These contexts were:

- patients with background pain for whom oral opioid treatment is suitable (see sections 3.3 and 3.4)
- patients with background pain for whom oral opioid treatment is not suitable (see sections 3.5, 3.6 and 3.7)
- patients who need opioid treatment to control breakthrough pain after receiving opioids for background pain (see section 3.8).

3.3 Starting strong opioids – titrating the dose with immediate-release, sustained-release or transdermal patches

This section deals with initiation of strong opioids in patients who are able to take oral medication. It compares oral immediate-release preparations with oral sustained-release preparations or transdermal patches. In most patients with pain requiring strong opioids it will be necessary to titrate the starting dose to find the dose that gives the optimal balance of pain relief and side effects. In some patients with stable pain it may be possible to start with sustained-release preparations – for the comparison of sustained-release preparations (oral versus transdermal) see section 3.4.

3.3.1 Review question

- 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?

3.3.2 Evidence review

This review question focused on the effectiveness of immediate-release (IR) morphine or IR oxycodone compared with sustained-release (SR) morphine or SR oxycodone and compared with transdermal fentanyl or buprenorphine patches as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids. Papers were included if they compared either IR morphine or IR oxycodone with SR morphine, SR oxycodone, transdermal fentanyl patch or buprenorphine patches in this patient group, in a randomised controlled trial (RCT), or if they were systematic reviews of such trials. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question was on first-line treatment with strong opioids, some of the included studies included patients who had previously received strong opioids. In such cases, the evidence quality was downgraded for indirectness (see tables 3 and 4). When possible, meta-analyses were conducted; although the possibility of subgroup analyses was explored based on IR and SR drug (morphine or oxycodone), type of transdermal patch (fentanyl or buprenorphine) and population (cancer or non-cancer), no subgroup analyses were conducted because this was not feasible.

Immediate-release opioids compared with sustained-release opioids

Immediate-release morphine compared with sustained-release morphine

Twenty-one RCTs compared IR morphine with SR morphine, eight of which were included in abstract form (Dalton et al. 1989; Deng et al. 1997; Levy et al. 1993; MacDonald et al. 1987; Poulain et al. 1990; Ranchere et al. 1991; Walsh 1985; Xu et al. 1995) while the remainder were full-text publications (Arkinstall et al. 1989; Christrup et al. 1999; Cundiff et al. 1989; Deschamps et al. 1992; Finn et al. 1993; Gillette et al. 1997; Hanks et al. 1987; Klepstad et al. 2003; Knudsen et al. 1985; Panich and Charnvej 1993; Thirlwell et al. 1989; Ventafridda et al. 1989; Walsh et al. 1992). Table 2 lists the main characteristics of each of the included studies and the GRADE summary is shown in table 3. None of the studies found any differences in pain intensity or relief between IR and SR morphine (apart from Dalton et al. [1989], who

reported that 90 mg SR morphine gave improved analgesia compared with 30 mg IR morphine) and tended to find no differences in the occurrence of side effects or adverse events (Arkinstall et al. 1989; Christrup et al. 1999; Deschamps et al. 1992; Finn et al. 1993; Gillette et al. 1997; Levy et al. 1993; MacDonald et al. 1987; Panich and Charnvej 1993; Poulain et al. 1990; Ranchere et al. 1991; Thirlwell et al. 1989; Walsh 1985; Walsh et al, 1992) with the following exceptions: Ventafridda et al. (1989) reported that compared with IR morphine, SR morphine was associated with lower daily rates of itching, dry mouth, drowsiness, nausea, vomiting, headache, and constipation. Hanks et al. (1987) reported some differences between IR and SR morphine in terms of alertness (IR better) and sleep (SR better), but both of these differed between the groups at baseline. Dalton et al. (1989) found that 90 mg SR morphine resulted in increased toxicity compared with 30 mg IR morphine. Knudsen et al. (1985) showed some suggestion that sedation rates were higher at days 1–3 (combined) in SR morphine compared with IR morphine. And Klepstad et al. (2003) reported that patients titrated with IR morphine reported significantly more tiredness at the end of titration compared with patients titrated with SR morphine. Neither of the two studies that reported health-related quality of life found any differences between IR and SR morphine treatment (Klepstad et al. 2003; Ranchere et al. 1991).

Immediate-release oxycodone compared with sustained-release oxycodone

Four RCTs compared IR oxycodone with SR oxycodone, all of which were full-text publications (Kaplan et al. 1998; Parris et al. 1998; Salzman et al. 1999; Stambaugh et al. 2001). Table 2 lists the main characteristics of each of the included studies and the GRADE summary is shown in table 4. None of the studies found any differences in pain intensity or relief between IR and SR oxycodone and none of the studies reported individually that the oxycodone formulations differed in rates of side effects or adverse events, apart from Kaplan et al. (1998) who found that SR oxycodone was associated with fewer side effects and adverse events than IR oxycodone (including headache and those associated with the digestive system). Meta-analyses of the observed side effects in three of the four RCTs (Kaplan et al. 1998; Parris et al. 1998; Salzman et al. 1999) confirmed that no differences were evident in the rate of

side effects or adverse events between IR and SR oxycodone (see also table 1 and the forest plots in appendix E). The results of the remaining RCT (Stambough et al. 2001) were not included in the meta-analysis due to its cross-over design.

Immediate-release opioids compared with transdermal patches

No RCT evidence was identified for the comparison between IR morphine or oxycodone and fentanyl or buprenorphine patches.

Table 2 Summary of included studies comparing immediate-release opioids with sustained-release opioids or with transdermal patches for first-line treatment of pain

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Arkinstall et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 29 patients aged ≥ 19 years with an analgesic regimen ≥ 60 mg/day of oral morphine	Sustained-release morphine v immediate-release morphine	Pain intensity, supplemental morphine, side effects, patient preference
Christrup et al. (1999)	Randomised, double-blind/double-dummy, cross-over study	N = 18 outpatients with severe cancer-related pain who were stabilised on oral morphine	Sustained-release morphine v immediate-release morphine	Pain intensity, sedation, side effects
Cundiff et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 23 adult patients with chronic cancer pain	Sustained-release morphine v immediate-release morphine	Pain intensity, pain frequency, rescue medication, side effects
Dalton et al. (1989)	RCT (parallel groups; abstract)	N = 68 with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain relief, side effects
Deng et al. (1997)	RCT (parallel groups; abstract)	N = 17 cancer patients with moderate-severe pain	Sustained-release morphine v immediate-release morphine	Pain relief
Deschamps et al. (1992)	Randomised, double-blind/double-dummy, cross-over study	N = 20 adult patients with pain from metastatic cancer and normal haematologic, hepatic and renal function	Sustained-release morphine v immediate-release morphine	Pain intensity, supplemental immediate-release morphine, side effects
Finn et al. (1993)	Randomised, double-blind/double-dummy, cross-over study	N = 37 adult outpatients with pain from advanced cancer requiring a stable daily dose ≥ 60 mg immediate-release morphine with a life expectancy > 1 week and	Sustained-release morphine v immediate-release morphine	Analgesic efficacy, breakthrough pain, side effects

		< 6 months.		
Gillette et al. 1997	Randomised, double-blind/double-dummy, cross-over study	N = 35 adult patients with end-stage cancer and normal renal and hepatic function	Sustained-release morphine v immediate-release morphine	Pain intensity, adverse events, side effects
Hanks et al. (1987)	Randomised, double-blind/double-dummy, cross-over study	N = 27 patients with advanced cancer admitted to hospital for continuing care with pain that was controlled by immediate-release morphine and who had received the same dose of morphine for ≥ 7 days	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects
Kaplan et al. (1998)	RCT (parallel groups)	N = 164 patients treated with a strong single entity opioid or 10 or more tablets per day of a fixed-dose opioid/non-opioid analgesic who were receiving a stable opioid dose and had stable coexistent disease	Sustained-release oxycodone v immediate-release oxycodone	Pain intensity, discontinuation, side effects
Klepstad et al. (2003)	RCT (parallel groups)	N = 40 adult patients with chronic cancer pain despite ongoing treatment for weak to mild pain	Sustained-release morphine v immediate-release morphine	Time to acceptable pain relief, pain intensity, side effects, health-related quality of life
Knudsen et al. (1985)	Randomised, double-blind/double-dummy, cross-over study	N = 18 patients with ≥ 7 days of well-functioning regular treatment immediate-release morphine for moderate-severe pain from metastatic/invasive cancer which was not rapidly progressing and physically and psychologically able to maintain a fixed dosage schedule and to complete	Sustained-release morphine v immediate-release morphine	Pain, sedation, side effects, patient preference

		questionnaires at fixed time points throughout a 2-week period		
Levy et al. (1993)	RCT (parallel groups; abstract)	N = 65 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects, adverse events
MacDonald et al. (1987)	Randomised, double-blind, cross-over study (abstract)	N = 28 patients with advanced cancer receiving narcotics for the treatment of stable cancer pain	Sustained-release morphine v immediate-release morphine	Pain intensity, supplementary morphine, side effects
Panich and Charnvej.(1993)	Randomised, single-blind (assessor), cross-over study without placebo control	N = 23 cancer patients referred to pain clinic	Sustained-release morphine v immediate-release morphine	Pain intensity, sleep duration, side effects, patient preference
Parris et al. (1998)	RCT (parallel groups)	N = 111 adult cancer patients receiving 6–12 tablets or capsules a day of fixed-combination analgesics (opioid/non-opioid) for cancer-related pain with stable coexistent disease	Sustained-release oxycodone v immediate-release oxycodone	Pain intensity, discontinuation, side effects
Poulain et al. (1990)	Open-label, randomised, cross-over study (abstract)	N = 84 patients with cancer pain	Sustained-release morphine v immediate-release morphine	Patient preference, pain control, side effects
Ranchere et al. (1991)	Multicentre, randomised, double-blind/double-dummy, cross-over study (abstract)	N = 52 patients with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, quality of life, adverse events, patient preference
Salzman et al. (1999)	RCT (parallel groups)	N = 47 adult patients with stable chronic pain not adequately controlled by prior analgesic therapy with or without opioids	Sustained-release oxycodone v immediate-release oxycodone	Stable analgesia, time to stable analgesia, pain intensity Adverse events
Stambaugh et al.	Randomised, double-	N = 40 adults with moderate or	Sustained-release	Pain relief, side effects

(2001)	blind, cross-over study	severe cancer-related pain able to take oral medication	oxycodone v immediate-release oxycodone	
Thirlwell et al. (1989)	Randomised, double-blind/double-dummy, cross-over study	N = 23 adult patients requiring opal opioid therapy for cancer-related pain and mentally and physically competent to comply with therapeutic protocol	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects, supplemental morphine
Ventafridda et al. (1989)	RCT (parallel groups)	N = 70 patients with pain from advanced cancer	Sustained-release morphine v immediate-release morphine	Pain intensity, side effects
Walsh (1985)	Randomised, double-blind/double-dummy, cross-over study (abstract)	N = 36 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, side effects
Walsh et al. (1992)	Randomised, double-blind/double-dummy, cross-over study	N = 33 adults with cancer-related pain	Sustained-release morphine v immediate-release morphine	Pain, side effects
Xu et al. (1995)	RCT (parallel groups; abstract)	N = 262 cancer patients with moderate-severe pain	Sustained-release morphine v immediate-release morphine	Pain intensity, pain relief
Abbreviations: CI, confidence interval; RCT, randomised controlled trial; v, versus.				

Table 3 GRADE profile summary comparing immediate-release morphine with sustained-release morphine for first-line treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Immediate-release morphine	Relative (95% CI)	Absolute	
Pain											
21[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	883[d]	729[d]	Not pooled. No differences reported		⊕⊕OO LOW
Side effects/adverse events											
18[e]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	693[d]	593[d]	Not pooled. Some differences reported within some of the studies		⊕⊕OO LOW
(Health-related) quality of life											
2[f]	Randomised trials	Serious[g]	No serious inconsistency	Serious[h]	Serious[g]	None	71[j]	67[j]	Not pooled. No differences reported		⊕OOO VERY LOW

[a] Published as full text: Arkinstall et al. (1989); Christrup et al. (1999); Cundiff et al. (1989); Deschamps et al. (1992); Finn et al. (1993); Gillette et al. (1997); Hanks et al. (1987); Klepstad et al. (2003); Knudsen et al. (1985); Panich and Charnvej (1993); Thirlwell et al. (1989); Ventafridda et al. (1989); Walsh et al. (1992). Published as abstracts Dalton et al. (1989); Deng et al. (1997); Levy et al. (1993); MacDonald et al. (1987); Poulain et al. (1990); Ranchere et al. (1991); Walsh (1985); Xu et al. (1995).

[b] N = 8 of the studies were only in abstract form and could not therefore be fully evaluated. The quality of the studies reported in full varied (e.g., unclear methods of allocation concealment and randomisation, Intention-to-treat analysis not always performed).

[c] Not all first-line treatment.

[d] The majority of the included studies were of cross-over design, which means that patients were counted in both treatment groups.

[e] Arkinstall et al. (1989); Christrup et al. (1999); Dalton et al. (1989); Deschamps et al. (1992); Finn et al. (1993); Gillette et al. (1997); Hanks et al. (1987); Klepstad et al. (2003); Knudsen et al. (1985); Levy et al. (1993); MacDonald et al. (1987); Panich and Charnvej (1993); Poulain et al. (1990); Ranchere et al. (1991); Thirlwell et al. (1989); Ventafridda et al. (1989); Walsh et al. (1985, 1992)

[f] Klepstad et al. (2003), Ranchere et al. (1991).

[g] One of the studies was in abstract form only.

[h] Unclear if it was first-line treatment in all patients.

[i] Small N.

[j] One of the two included studies was of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

Table 4 GRADE profile summary comparing immediate-release oxycodone with sustained-release oxycodone for first-line treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release oxycodone	Immediate-release oxycodone	Relative (95% CI)	Absolute	
Pain											
4[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	184[d]	188[d]	Not pooled. No differences reported		⊕⊕OO LOW
Side effects/adverse events											
4[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	184[d]	188[d]	No differences reported		□□□□ LOW

[a] Kaplan et al. (1998); Parris et al. (1998); Salzman et al. (1999); Stambaugh et al. (2001).

[b] None of the studies reported the randomisation procedure or allocation concealment adequately.

[c] Not all first-line treatment.

[d] One of the included studies was of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

3.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Immediate-release opioids compared with sustained-release opioids

3.3.3.1 *Immediate-release morphine is associated with no differences in pain relief/intensity (in 21 out of 21 studies; LOW QUALITY), no differences in rates of side effects or adverse events (in 13 out of 18 studies; LOW QUALITY) and no differences in health-related quality of life (in two out of two studies; VERY LOW QUALITY) compared with sustained-release morphine.*

3.3.3.2 *Immediate-release oxycodone is associated with no differences in pain relief/intensity (in four out of four studies; LOW QUALITY) and no differences in rates of side effects/adverse events (in four out of four studies; LOW QUALITY) compared with sustained-release oxycodone.*

Immediate-release opioids compared with transdermal patches

3.3.3.3 *No RCT evidence identified.*

3.3.4 Health economic modelling

There is no significant cost difference between immediate-release and sustained-release opioids (for example, immediate-release morphine is only £0.28 more expensive than sustained-release morphine per 100 mg). In addition, the dose-finding process will only last for a few days. After the initial optimal dose has been found, virtually all patients will start to receive sustained-release opioids.

Because the cost difference between alternative interventions is very small, this topic is considered a low priority for economic analysis.

The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.3.5 Evidence to recommendations

The aim of this topic was to determine the most effective formulation of opioid (immediate- or sustained-release) for dose titration by comparing the effectiveness of immediate-release morphine or oxycodone with sustained-release morphine or oxycodone and the effectiveness of immediate-release morphine or oxycodone with a transdermal patch formulation (either fentanyl or buprenorphine). For both of these analyses the GDG considered the outcomes of pain, opioid side effects, adverse events, percentage of patients switching opioid and health-related quality of life to be the most clinically relevant.

No RCT evidence was found for the comparison of immediate-release opioid with transdermal patch formulation and therefore no outcomes were reported.

For the comparison of immediate-release and sustained-release opioids, evidence was reported for the outcomes of pain, opioid side effects, adverse events and health-related quality of life. No evidence was found for the percentage of patients switching opioid. The overall quality of the evidence across each of these outcomes was low or very low (health-related quality of life) as assessed by GRADE.

Although not specified in the question, the GDG also considered which opioid is more effective in the initial titration phase and in the subsequent maintenance phase. The evidence was of low quality and difficult to interpret, however the GDG concluded that an immediate-release opioid and a sustained-release opioid had equivalent efficacy in both the titration and maintenance phases.

No formal cost-effectiveness analysis was conducted for this question. The GDG noted that an immediate-release opioid may be more costly because it has to be administered every 4 hours. The GDG also agreed the cost may vary depending upon setting (for example, a patient self-administering, or visiting their GP). However, the GDG concluded that the overall cost impact may not be significant because an immediate-release opioid would only be administered over a short time period.

From the available evidence, the GDG was unable to recommend a particular formulation of opioid because both immediate- and sustained-release formulations showed equivalence for all the reported outcomes. The GDG agreed that offering patients a choice of immediate- or sustained-release formulations would be likely to improve adherence because patients would be able to choose the formulation that was most acceptable to them. Based on their clinical experience, the GDG also agreed to recommend a rescue dose of immediate-release opioid when required, to minimise pain in the titration phase and hopefully improve patients' quality of life.

Because no evidence was identified in the literature to compare immediate-release opioid and transdermal patches, the GDG was unable to make a recommendation on the use of transdermal patches as a first-line treatment.

The GDG noted that specific dosing guidance would be helpful to reduce the potential harms of inappropriate doses of opioids being used by inexperienced practitioners. The GDG therefore recommended, based on its clinical experience and manufacturers' guidelines, safe starting doses of morphine when initiating treatment. The GDG also agreed that frequent review would be needed during the titration phase to ensure a balance between pain control and side effects.

The GDG was aware of the importance of prescribing rescue medication for breakthrough pain that may occur during the titration phase. Therefore the recommendation from section 3.8 was incorporated into this recommendation.

3.3.6 Recommendations on first-line treatment – starting strong opioids

Recommendation 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.

Recommendation 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, **with**
- 5 mg oral immediate-release morphine for rescue doses during the titration phase.

Recommendation 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.

Recommendation 1.1.7

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

3.4 First-line maintenance treatment

This section deals with the management of background pain that requires the regular prescription of a strong opioid.

3.4.1 Review question

- 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?

3.4.2 Evidence review

This review question focused on the effectiveness of sustained-release (SR) morphine compared with SR oxycodone, transdermal fentanyl or buprenorphine patches, as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids. Papers were included if they compared SR morphine with SR oxycodone, transdermal fentanyl patch or buprenorphine patch in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 5 lists the main characteristics of each of the included studies. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question is on first-line maintenance treatment with strong opioids, some of the included studies were not in strong-opioid-naive patients. In such cases, the evidence quality was downgraded for indirectness (see tables 6–8). If feasible, meta-analyses with possible subgroup analysis based on the population (cancer or non-cancer) were anticipated, but the body of evidence consisted of five studies, four of which contained pooled analyses (three of these studies were systematic reviews). Therefore no further pooled analyses were performed.

Sustained-release morphine compared with sustained-release oxycodone

Bekkering et al. (2011) conducted a systematic review with network meta-analysis of RCTs on patients with chronic pain from cancer or non-cancer conditions and found that pain did not differ between the treatments regardless of treatment duration (1 day to 1 week, 1 week to 1 month, over 1 month) and when the analyses were limited to the studies on cancer pain. However, in patients with non-cancer pain, SR morphine was significantly more effective than SR oxycodone. In the studies on cancer pain, treatment discontinuation (for any reason, because of lack of efficacy, or because of adverse events) did not differ between the treatments. In a systematic review without meta-analysis, Caraceni et al. (2011) reported that a cross-over trial comparing SR morphine with SR oxycodone found no difference in pain between the treatments. However, SR morphine was associated with more nausea and vomiting. In a set of meta-analyses of four RCTs (one of which compared SR oxycodone with SR hydromorphone), Reid et al. (2006) found no differences between the treatments in pain intensity, nausea, constipation, drowsiness (analyses excluded the hydromorphone trial), concentration difficulty, hallucinations, vomiting, agitation, dizziness, poor sleep, fatigue, itch, vivid dreams, headache and sweating. There was some suggestion that SR morphine was associated with higher rates of dry mouth compared with SR oxycodone. See GRADE table 6.

Sustained-release morphine compared with transdermal patches

Sustained-release morphine compared with transdermal fentanyl patch

Network meta-analyses conducted by Bekkering et al. (2011) on data from patients with chronic pain from cancer or non-cancer conditions showed that pain did not differ between the treatments when the treatment duration was 1 day to 1 week, or over 1 month, and in patients with non-cancer pain. However, with treatment duration of 1 week to 1 month and when the analyses were limited to the studies on cancer pain, SR morphine was significantly more effective than transdermal fentanyl. In the studies on cancer pain, the odds of treatment discontinuation for any reason and because of adverse events, but not because of lack of efficacy, were reduced in patients

receiving transdermal fentanyl compared with those receiving SR morphine (odds ratios = 0.43 and 0.12 respectively). One further study included in the systematic review but not the network meta-analyses of Bekkering et al. (2011) found no difference in pain intensity, nausea or vomiting, urinary retention and urticaria between the treatments, although SR morphine was associated with higher rates of constipation. In a systematic review without meta-analysis, Caraceni et al. (2011) reported that a cross-over trial comparing SR morphine with transdermal fentanyl found no difference in pain between the treatments. The side-effects data from this study are included in Tassinari et al. (2008). Meta-analyses of data extracted by Tassinari et al. (2008) from three RCTs showed that of overall side effects, overall gastrointestinal side effects, nausea, constipation, overall neurological side effects, drowsiness, patient preference and hypoventilation, only constipation and patient preference were found to differ between SR morphine and transdermal fentanyl, both favouring transdermal fentanyl (odds ratios = 2.35 and 2.32 respectively). Zuurmond and Davis (2002) reported in an abstract that although pain control and the overall impression were equivalent between SR morphine and transdermal fentanyl, transdermal fentanyl was rated more convenient to use and associated with fewer side effects.

Sustained-release morphine compared with transdermal buprenorphine patch
The network meta-analyses by Bekkering et al. (2011) showed that, in patients with treatment duration of 1 week to 1 month, SR morphine was significantly more effective in reducing pain intensity compared with transdermal buprenorphine. However, with treatment duration of over 1 month and in patients with cancer pain, transdermal buprenorphine was significantly more effective than SR morphine. The odds of treatment discontinuation for any reason, but not because of lack of efficacy, were reduced in patients receiving transdermal buprenorphine compared with those receiving SR morphine (odds ratio = 0.11). Analyses of data extracted by Tassinari et al. (2008) from one RCT showed that of overall side effects, overall gastrointestinal side effects, nausea, constipation, overall neurological side effects and drowsiness, only overall gastrointestinal side effects and constipation were found to differ between SR morphine and transdermal

buprenorphine, both favouring transdermal buprenorphine (odds ratios = 4.79 and 7.5 respectively).

For the review protocol and inclusion and exclusion criteria, and full list of excluded papers, please see appendix D.

Table 5 Summary of included studies comparing sustained-release morphine with sustained-release oxycodone or with transdermal patches

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Bekkering et al. (2011)	Systematic review of RCTs (excluding cross-over trials) with network meta-analysis	N = 56 (10 of which were directly relevant to the present question) RCTs that evaluated the efficacy or tolerability of step III opioids in adult patients with cancer-related or non-cancer-related chronic pain. Studies had to compare an oral or transdermal step III opioid with placebo or with another step III opioid and report on ≥ 1 of the pre-specified outcomes of efficacy	Sustained-release morphine v sustained-release oxycodone; sustained-release morphine v transdermal fentanyl; sustained-release morphine v transdermal buprenorphine	Pain intensity, treatment discontinuation
Caraceni et al. (2010)	Systematic review of RCTs (including cross-over trials) without meta-analysis	N = 2 RCTs conducted in adult patients with chronic cancer pain reporting data on patient reported efficacy and/or side effects of morphine administered orally in comparison with placebo or other opioids written in English	Sustained-release morphine v sustained-release oxycodone; sustained-release morphine v transdermal fentanyl	Efficacy, side effects
Reid et al. (2006)	Systematic review of RCTs (including cross-over trials) with meta-analysis	N = 4 RCTs comparing oxycodone with an active analgesic drug in patients with cancer-related pain. All routes of drug administration and all formulations of oxycodone were considered	Sustained-release morphine v sustained-release oxycodone; sustained-release oxycodone v sustained-release hydromorphone	Pain intensity, adverse events
Tassinari et al. (2008)	Systematic review of RCTs (including cross-	N = 4 phase III RCTs comparing sustained-release morphine with	Sustained-release morphine v transdermal	Adverse effects, patient preference, trial

	over trials) with meta-analysis	transdermal opiates in patients with moderate-severe cancer pain with a defined need for opiates at the time of entering the trial	fentanyl; sustained-release morphine v transdermal buprenorphine	withdrawal
Zuurmond and Davis (2002)	Pooled analysis of 2 open-label RCTs (parallel groups; abstract)	Strong opioid-naive patients and patients transferring from weak to strong opioids. No further details reported	Sustained-release morphine v transdermal fentanyl	Pain, side effects
Abbreviations: RCT, randomised controlled trial; v, versus.				

Table 6 GRADE profile summary comparing sustained-release morphine with sustained-release oxycodone for first-line maintenance treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Sustained-release oxycodone	Relative (95% CI)	Absolute	Quality
Pain											
9[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	none	See table 5, text in section 3.4.2 and footnote a.		No differences reported in cancer patients. See also text in section 3.2.8.1		□□□□ LOW
Side effects											
5[d]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	none	199[e]	195[e]	Meta-analysis of 4 trials found no differences. See also text in section 3.2.8.1		□□□□ LOW

[a] This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualifications: One of the meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006) and the other meta-analysis was a network meta-analysis with an overall total of 56 studies (Bekkering et al., 2011).

[b] Some limitations in the included studies (for example, unclear methods of sequence generation and allocation concealment, no blinding, inadequate assessment of outcome data, funding from pharmaceutical companies).

[c] Not all studies on population/intervention of interest.

[d] This is the number of direct trials from one meta-analysis (Reid et al., 2006) and one systematic review (Caraceni et al., 2011) with the following qualification: The meta-analyses also included a trial comparing hydromorphone with oxycodone (Reid et al., 2006).

[e] The majority of the included studies were of cross-over design, which means that patients were counted in both treatment groups.

Abbreviations: CI, confidence interval.

Table 7 GRADE profile summary comparing sustained-release morphine with transdermal fentanyl for first-line maintenance treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Transdermal fentanyl	Relative (95% CI)	Absolute	Quality
Pain											
8[a]	Randomised trials	Serious[b]	No serious inconsistency[c]	Serious[d]	No serious imprecision	None	See text in section 3.4.2 and footnote a		4/8 studies favoured morphine[e]. 4/8 studies reported no difference. See also text in section 3.2.8.1		⊕⊕OO LOW
Side effects (excluding constipation)											
6[f]	Randomised trials	Serious[b]	No serious inconsistency[c]	Serious[d]	No serious imprecision	None	> 311[g]	> 314[g]	No specific differences reported		⊕⊕OO LOW
Constipation											
6[f]	Randomised trials	Serious[b]	No serious inconsistency	Serious[d]	No serious imprecision	None	> 311[g]	> 314[g]	No differences reported		⊕⊕OO LOW

[a] This is the number of direct trials from one pooled analysis (Zuurmond & Davis, 2002) and two systematic reviews (Bekkering et al., 2011, Caraceni et al., 2011), one of which was a network meta-analysis with an overall total of 56 studies (Bekkering et al., 2011).

[b] One study reported in abstract form only. Other studies subject to different limitations (e.g., unclear methods of sequence generation and allocation concealment, no blinding, inadequate assessment of outcome data).

[c] Some discrepancy between results from three individually reported studies and the network meta-analysis.

[d] Not all first-line treatment.

[e] This is the result from the network meta-analysis on patients with cancer pain.

[f] This is the number of direct trials from one pooled analysis (Zuurmond & Davis, 2002) and two systematic reviews (Bekkering et al., 2011, Tassinari et al., 2008),

[g] One of the included studies was a cross-over trial, therefore the patients were counted in both groups. One of the included papers (Zuurmond et al. 2002) did not report the number of patients.

Abbreviations: CI, confidence interval.

Table 8 GRADE profile summary comparing sustained-release morphine with transdermal buprenorphine for first-line maintenance treatment of pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sustained-release morphine	Transdermal buprenorphine	Relative (95% CI)	Absolute	
Pain											
1[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	Serious[d]	none	26[e]	26[e]	Weighted mean difference = −16.4 (favours buprenorphine)[f]. See also text in section 3.4.2		⊕OOO VERY LOW
Side effects (excluding overall gastrointestinal side effects and constipation)											
1[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	Serious[d]	none	26[e]	26[e]	No differences reported. See also text in section 3.2.8.1		⊕OOO VERY LOW
Overall gastrointestinal side effects and constipation											
1[a]	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	Serious[d]	none	26[e]	26[e]	Favour transdermal buprenorphine: ORs = 4.79 and 7.5 respectively		⊕OOO VERY LOW

[a] This is the number of direct trials from two meta-analyses (Bekkering et al., 2011; Tassinari et al., 2008) with the following qualification: One of the meta-analyses was a network meta-analysis with an overall total of 56 studies.

[b] Using the Jadad scoring system, Tassinari et al. (2008) graded this study 2/5.

[c] Tramadol was added to the interventions in both groups. Unclear if first-line.

[d] Low N.

[e] This is the number of patients in the direct trial from the two meta-analyses, of which was a network meta-analysis with an overall total of 56 studies.

[f] This is the result from the analysis on patients with cancer pain.

Abbreviations: CI, confidence interval; OR, odds ratio.

3.4.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Sustained-release morphine compared with sustained-release oxycodone

3.4.3.1 *Sustained-release morphine is associated with no differences in pain relief in patients with cancer pain (in nine out of nine studies; LOW QUALITY) and differences in side effect profiles (in four out of five studies; LOW QUALITY) compared with sustained-release oxycodone.*

Sustained-release morphine compared with transdermal fentanyl patch

3.4.3.2 *Sustained-release morphine is associated with either better (in four out of eight studies; LOW QUALITY) or comparable (in four out of eight studies; LOW QUALITY) pain relief in patients with cancer pain and is associated with higher odds of constipation (in six out of six studies; LOW QUALITY), but no other side effects (in four out of six studies; LOW QUALITY) compared with transdermal fentanyl.*

Sustained-release morphine compared with transdermal buprenorphine patch

3.4.3.3 *Sustained-release morphine provides worse pain relief in patients with cancer pain (weighted mean difference = −16.4) and is associated with higher odds of overall gastrointestinal side effects (odds ratio = 4.79) and constipation (odds ratio = 7.5), but no other side effects (in one out of one study; VERY LOW QUALITY) compared with transdermal buprenorphine.*

3.4.4 Health economic modelling

Background and aims

Patients with advanced and progressive disease who have tried non-opioid analgesics and opioids conventionally used in the treatment of moderate pain but these have not worked are indicated to receive strong opioids. However, there is uncertainty over the choice of strong opioids for the maintenance treatment of background pain.

The most commonly used treatment is oral sustained-release morphine, primarily because it is cheap and easy for the patients to take. However, recently, the use of transdermal patches (fentanyl and buprenorphine) has increased substantially as a first-line approach to moderate-to-severe pain. Transdermal patch treatment may be preferred over oral treatment because of better patient adherence, fewer treatment-related adverse events and the preference of the patient.

This economic evaluation aimed to assess the cost effectiveness of first-line opioid treatments in patients with advanced and progressive disease who require strong opioids. The analysis considered the perspective of the NHS.

Methods

Economic evidence review

A systematic literature review was performed to assess the current economic literature. Three relevant studies were identified: Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006). Each of these studies described the development of an economic model to assess the cost effectiveness of oral opioids. Health effects were quantified in terms of quality-adjusted life days (QALDs) and/or quality-adjusted life years (QALYs).

All of the studies were based around the same model structure. Lehmann et al. (2002) and Greiner et al. (2006) used the same basic model structure employed in the study by Neighbors et al. (2001). Of the three papers, two considered a German perspective (Lehmann et al. 2002 and Greiner et al. 2006), while the remaining study considered a US perspective (Neighbors et al. 2001).

All the studies found transdermal fentanyl to be cost effective compared with oral sustained-release morphine, with incremental cost-effectiveness ratios (ICERs) of £17,798, £14,487 and £1406 per QALY gained in the studies by Neighbors et al. (2001), Lehmann et al. (2002) and Greiner et al. (2006) respectively. In addition, Greiner et al. (2006) showed transdermal buprenorphine to be cost effective compared with oral sustained-release morphine with an ICER of £6248 per QALY gained.

All three of the studies were deemed only partially applicable to the guideline. This was mostly a result of the studies considering countries other than the UK. In some instances, there were also concerns about the applicability of the quality of life data because they were often based on assumptions by a panel of clinical experts rather than reported directly from patients. Furthermore, potentially serious limitations were identified with all of the included studies. Many of the key model parameters, such as efficacy and resource use, were estimated using the opinion of a panel of clinical experts. In addition, potential conflicts of interest were identified in all of the studies, because the analyses were sponsored by pharmaceutical companies.

De novo economic model

Because the current economic literature didn't adequately address the decision problem, a de novo economic model was developed to assess the cost effectiveness of first-line strong opioid treatments.

The results of the clinical review were used to inform the economic model. The review suggested that the proportion of patients attaining pain relief may differ between treatments, depending on the patient population and time period considered (Tassinari et al. 2008). Furthermore, the review showed that there were no statistically significant differences in the proportion of patients who discontinue as a result of a lack of efficacy. It was therefore assumed that all treatments were equally effective (in terms of pain relief).

However, the clinical review did show differences in the side-effect profiles of the drugs. Significant reductions in constipation were observed in those patients receiving transdermal treatment compared with oral sustained-release morphine (Tassinari et al. 2008). In addition, patients receiving transdermal buprenorphine patch had significantly fewer gastrointestinal side effects than patients receiving oral sustained-release morphine (Tassinari et al. 2008). However, the comparison of oral sustained-release morphine and transdermal buprenorphine patch was based on a study with low patient numbers (N = 52) and was judged to be of very low quality. Therefore, given the limitations of the evidence base for oral sustained-release morphine and

transdermal buprenorphine patch, it was decided that this comparison would not be considered in the economic evaluation.

Side-effect differences were also reported for the comparison of oral sustained-release morphine and oxycodone. According to Reid et al. (2006), oxycodone was associated with a reduction in the occurrence of dry mouth. However, this aspect was not considered in the cost-effectiveness analysis because it is unlikely to have any meaningful impact on costs and benefits. Lauretti et al. (2003) reported fewer nausea events with oxycodone but this was based on a very small study population (N = 22). Other studies in larger populations didn't show any significant differences in nausea (four out of five studies showed no statistically significant differences in side effects).

Given that oral sustained-release morphine and oral sustained-release oxycodone were equivalent in effectiveness terms, it was decided that this comparison would not need to be modelled. A decision on the most cost-effective treatment option could instead be based on the costs associated with each treatment.

Therefore, only the comparison of transdermal fentanyl patch and oral sustained-release morphine was considered in the economic model. A Markov model was developed to assess the cost effectiveness of transdermal fentanyl patch compared with oral sustained-release morphine.

Markov models involve dividing a patient's possible prognosis into a series of discrete health states. In this case, the health states were 'Receiving original opioids', 'Opioids terminated' and 'Switching'. All patients start in the 'Receiving original opioids' health state and at each weekly cycle may transit to the 'Switching' health state (following treatment discontinuation because of an adverse event) or the 'Opioids terminated' health state (following the spontaneous, non-treatment-related resolution of their pain symptoms), or they remain in the 'Receiving original opioids' health state.

Each of the health states has an associated cost and benefit tariff that patients accrue while in that state. The costs reflect the therapy that the patient is currently receiving. Thus, patients in the 'Receiving original opioids' state incur

the cost of the opioids that they started with, whereas there is no cost for patients in the ‘Opioids terminated’ state. Patients in the ‘Switching’ health state incur the cost of an alternative treatment, which is calculated as the average cost of the remaining treatments under comparison. For example, patients switching from oral sustained-release morphine incur an average of the cost of oral sustained-release oxycodone, transdermal fentanyl patch and transdermal buprenorphine patch. Patients in all health states incur the cost of a monthly GP visit, reflecting the regular monitoring of patients receiving strong opioids.

Patients on active treatment also incur the cost of concomitant laxatives, which are given to prevent the commonly experienced side effect of constipation. This is calculated as an average cost of the first line oral laxatives that are typically given (as identified by the GDG).

However, it is noted that patients receiving preventative laxatives may still experience constipation. In this event, patients incur the cost of further laxative treatments consisting of strong oral laxatives or suppositories. Following advice from the GDG, 10% of patients were estimated to require an enema and thus incurred the cost of enema treatments along with the administration cost (visit by community nurse).

The transition to the ‘Switching’ health state has a ‘one-off’ cost associated with administering the new treatment and monitoring the patient This cost includes the cost of a GP visit, a community nurse visit, advice from a medical consultant (sought by GP) and a follow-up phone call from the GP.

Costs were calculated using dose and unit cost information from the ‘British national formulary’ (‘BNF’), resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the GDG.

In terms of benefits, each health state has an associated quality of life (QoL) tariff. This reflects the model's measurement of benefits in terms of QALYs, whereby the quantity and quality of life can be expressed simultaneously. Patients in the ‘Receiving original opioids’ and ‘Switching’ health states receive a QoL value associated with controlled pain. Patients in the ‘Opioids

terminated' health state receive a utility value associated with reduced pain. Utility decrements are also applied to reduce QoL in those patients who experience adverse events. All utility estimates were sourced from published studies (Greiner W et al. 2006; Goossens M et al. 1999; Matza L et al. 2007; Belsey J et al. 2010; Ara R and Brazier J. 2008).

The overall costs and benefits for each treatment are then estimated on the basis of the total length of time patients spend in each health state over the time horizon that has been modelled. Given that the maximum modelled time horizon was 1 year, discount rates were not considered.

Results

The base-case results of the model are presented in table 9 for the comparison of oral sustained-release morphine compared with transdermal fentanyl patch. The results show the expected costs and benefits attained per patient over various time periods (up to 1 year). It can be seen that, at a threshold of £20,000 per QALY gained, transdermal fentanyl is not cost effective compared with oral sustained-release morphine at all time points.

Table 9 Base-case total expected costs, QALYs and ICERs for oral sustained-release morphine compared with transdermal fentanyl patch

Time point	Fentanyl		Morphine		Incremental		ICER
	Costs	QALYs	Costs	QALYs	Costs	QALYs	
1 month	£90	0.0452	£54	0.0449	£35	0.0003	£107,532
2 months	£178	0.0906	£107	0.0899	£71	0.0007	£109,469
3 months	£288	0.1474	£172	0.1463	£116	0.0011	£110,096
6 months	£573	0.2957	£342	0.2936	£231	0.0021	£110,268
12 months	£1,135	0.5950	£678	0.5908	£457	0.0042	£109,636
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year							

Sensitivity analysis

One-way sensitivity analysis showed the key drivers of the model to be the utility decrement associated with constipation, the discontinuation rate following a constipation event and the average dose used for maintenance treatment. However, the ICER remained above £20,000 per QALY gained in all scenarios modelled.

At the request of the GDG, threshold analysis was conducted on the switching cost required to attain cost effectiveness at a threshold of £20,000. The results showed that switching costs of £3,086 and £1,873 would be required when considering the base-case scenario and the scenario with an increased utility decrement (0.20) respectively. These were considerably higher than even the highest switching costs expected by the GDG members.

The results of the probabilistic sensitivity analysis showed that there was considerable variation around the mean cost-effectiveness result. However, at a threshold of £20,000 there was only an 8% probability that transdermal fentanyl patch would be cost effective compared with oral sustained-release morphine.

As with most economic evaluations, there are a number of limitations that should be acknowledged. Firstly, in clinical practice, the dose of strong opioids required for effective management of pain typically increases over time. In the model, an average maintenance dose was applied for the duration of the modelled time horizon. However, because of the relative prices of morphine and fentanyl, it is likely that including dose increases would only further improve the cost-effectiveness of morphine.

Secondly, the assumption that patients can only switch once implies that the second treatment that a patient receives is effective and well tolerated. Clearly, this may not be the case in clinical practice but the assumption was a necessary simplification. The likely influence of this assumption is somewhat difficult to ascertain but it is possible that allowing for multiple switches would improve the cost-effectiveness of transdermal fentanyl patch.

3.4.5 Evidence to recommendations

The aim of this topic was to determine the most effective first-line maintenance treatment for patients with advanced and progressive disease for whom treatment with oral opioids is suitable.

The GDG considered the outcomes of pain and opioid side effects to be the most important. Health-related quality of life was also considered an important outcome but was not reported in the evidence.

The overall evidence quality for both pain relief and rates of side effects was very low to low, as assessed by GRADE, for all outcomes considered. The GDG was aware that the low evidence grading related to design limitations, indirectness and imprecision (some studies only included low patient numbers). Despite these limitations the GDG agreed that the results from trials were generally consistent; therefore, the GDG felt confident in making a firm recommendation. In addition, the GDG felt that if more direct trial evidence was available this would be unlikely to change the direction and magnitude of results.

The GDG noted that based on the evidence, morphine is an effective and inexpensive opioid analgesic. Although the use of morphine may result in a small increase in gastrointestinal side effects compared with transdermal patches, the GDG agreed that these could be managed by adjunctive treatments. The GDG also agreed that the use of more costly preparations would need to be justified by evidence of superior efficacy or lower side-effect burden. However, studies comparing the effectiveness of fentanyl, buprenorphine and oxycodone with morphine were of poor quality and, in the opinion of the GDG, failed to demonstrate superiority over morphine. Studies suggested that the transdermal patches may be associated with fewer gastrointestinal side effects than morphine but the benefit conferred by fentanyl was not shown to be cost effective by cost-effectiveness analysis with an ICER of £107,532 per QALY gained at 1 month. The GDG noted that the evidence comparing morphine and buprenorphine consisted of only one study, which was very low quality and had low patient numbers. Because of these limitations the GDG was uncertain of the validity of the results and cost-effectiveness modelling was therefore not carried out for this comparison. The evidence showed that morphine and oxycodone have a similar side-effect profile; however, because oxycodone is more expensive, cost-effectiveness modelling was not conducted.

Consequently, the GDG decided to recommend oral sustained-release morphine as first-line maintenance treatment for patients with advanced and progressive disease who require strong opioids. It was also agreed that transdermal patch formulations should not be used routinely as first-line maintenance treatment.

The GDG noted that sensitivity analyses carried out in the health economic model, which were used to evaluate the magnitude of effect that would need to be seen in order to make transdermal patches cost effective compared with morphine, could not identify any clinically relevant scenario in which this would be the case. The GDG did not recommend further research in this area because it felt that if more direct trial evidence was available this would be unlikely to change the direction and magnitude of results.

3.4.6 Recommendations on first-line maintenance treatment

Recommendation 1.1.8

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

Recommendation 1.1.9

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

Recommendation 1.1.10

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

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

This section relates to patients who cannot safely swallow oral medication or have impaired absorption from the gastrointestinal tract, for example due to nausea and vomiting. The decision to use either the transdermal route or a subcutaneous infusion (see section 3.6) will depend on clinical assessment – including whether the pain is stable or unstable, the place of care (hospital or community), the resources available, and the need for co-administration of other drugs such as anti-emetics.

3.5.1 Review question

- 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?

3.5.2 Evidence review

This review question focused on the effectiveness of transdermal fentanyl patches compared with 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. Papers were included if they compared transdermal fentanyl patch treatment with transdermal buprenorphine patch treatment in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 10 lists the main characteristics of each of the included studies. For the review protocol, inclusion and exclusion criteria, and a full list of excluded papers, see appendix D.

Although the main focus of this question is on first-line treatment with strong opioids in patients in whom oral treatment is not suitable, some of the included studies were not in strong-opioid-naive patients and/or it was unclear whether oral treatment was suitable for the population. In such cases, the evidence quality was downgraded for indirectness (see table 11). If feasible, meta-

analyses with possible subgroups analysis based on the population (cancer or non-cancer) were anticipated. However, inspection of the body of evidence revealed that meta-analysis of the results was not feasible.

The search identified two studies comparing treatment with transdermal fentanyl with transdermal buprenorphine (Sarhan and Doghem.2009; Wirz et al. 2009). However, the study by Sarhan and Doghem (2009) was only published in abstract form and, instead of random assignment to treatment, the treatment groups in Wirz et al. (2009) consisted of randomly selected patients who were already receiving the study drugs. Sarhan and Doghem (2009) found no differences in pain, side effects, complications and treatment satisfaction between the treatment groups with the exception of drowsiness and local skin complications, which were higher in the buprenorphine group. Wirz et al. (2009) appeared to find comparable rates of constipation, defecation, nausea and vomiting between the treatments, but the interpretation of the results was hampered by the absence of statistical analyses comparing only fentanyl and buprenorphine.

Table 10 Summary of included studies comparing transdermal fentanyl patch with transdermal buprenorphine patch for first-line treatment of pain in patients for whom oral opioids are not suitable

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Sarhan and Doghem (2009)	RCT (parallel groups; abstract)	N = 32 opioid-naive patients suffering from chronic cancer pain with visual analogue scale (VAS) ≥ 7	Transdermal fentanyl patch v transdermal buprenorphine patch	Pain, side effects and complications
Wirz et al. (2009)	Prospective study with random selection of patients already receiving study medication for > 4 weeks	N = 116 patients with cancer-related pain, pure nociceptive pain, strictly ambulatory treatment, patient cooperation, and a score of 0–3 on the ECOG Performance Status scale	Transdermal fentanyl patch v transdermal buprenorphine patch	Constipation, nausea, vomiting
Abbreviations: RCT, randomised controlled trial; v, versus.				

Table 11 GRADE profile summary comparing transdermal fentanyl patch with transdermal buprenorphine patch for first-line treatment of pain in patients for whom oral opioids are not suitable

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Buprenorphine patch	Fentanyl patch	Relative (95% CI)	Absolute	
Pain											
1[a]	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	None	16	16	No difference reported		⊕OOO VERY LOW
Side effects											
2[d]	Randomised trials	Very serious[e]	No serious inconsistency	Serious[f]	No serious imprecision	None	77	71	Some differences reported. See also text in section 3.5.2		⊕OOO VERY LOW

[a] Sarhan et al. (2009)
[b] RCT published in abstract form only, so not possible to fully appraise.
[c] N = 32.
[d] Sarhan et al. (2009), Wirz et al. (2009)
[e] Studies either published in abstract form only or using randomly selected patients already receiving treatment drugs.
[f] Not all first-line treatment.
Abbreviations: CI, confidence interval.

3.5.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

3.5.3.1 Transdermal fentanyl is associated with no differences in pain relief (in one out of one study; VERY LOW QUALITY) and few differences in rates of side effects (in two out of two studies; VERY LOW QUALITY) compared with transdermal buprenorphine.

3.5.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.5.5 Evidence to recommendations

The aim of this topic was to determine the most effective transdermal patch for patients with advanced and progressive disease for whom treatment with oral opioids is not suitable.

The GDG considered the outcomes of pain relief, opioid side effects and adverse events to be the most important.

For the comparison of different transdermal patches, the overall quality of the evidence for both pain relief and rates of side effects was very low, as assessed by GRADE. The GDG was also aware that of the two studies appraised for this topic, one was only published in abstract form and the other had design limitations (instead of random assignment to treatment, the treatment groups consisted of randomly selected patients who were already receiving the study drugs).

Given that the evidence that was available was limited and of low quality, the GDG did not believe it was possible to make definitive recommendations on which transdermal patch should be offered to patients if oral opioid treatment was not suitable for them. However, the GDG recognised that while most patients in this category would have complex medical needs requiring specialist advice, there needed to be flexibility for experienced primary care

practitioners to offer alternative routes of administration if the analgesic requirements are stable. Therefore it recommended that transdermal patches should be considered.

The GDG considered that there might be potential additional costs from recommending specialist advice, but that there were also likely to be cost savings as a result of a reduction in inappropriate prescription of opioids. However, the GDG was uncertain of the cost implications of making this recommendation.

3.5.6 Recommendations on first-line treatment if oral opioids are not suitable – transdermal patches

Recommendation 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.

Recommendation 1.1.12

Use caution when calculating opioid equivalence for transdermal patches:

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

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

Where pain is unstable and opioid requirements need to be rapidly titrated a subcutaneous infusion can be used. This is not restricted to end-of-life care. Access to appropriate equipment and trained staff to administer the medication is essential.

3.6.1 Review question

- 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?

3.6.2 Evidence review

This review question focused on the effectiveness of subcutaneous morphine compared with 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. Papers were included if they compared subcutaneous morphine with subcutaneous diamorphine or with subcutaneous oxycodone treatment in this patient group, in an RCT, or if they were systematic reviews of such trials. However, the search identified no such papers.

3.6.3 Evidence statements

No evidence was identified on the effectiveness of subcutaneous morphine compared with 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.

3.6.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.6.5 Evidence to recommendations

The aim of this topic was to determine the most effective subcutaneous opioid for patients with advanced and progressive disease for whom treatment with oral opioids was not suitable. Unfortunately no evidence was found comparing these interventions. Despite this lack of evidence, the GDG recognised that guidance was needed on what formulation of opioid should be used when oral opioids are not suitable and patch formulations are not appropriate.

The GDG therefore agreed, based on its clinical experience, that subcutaneous opioids should be considered for patients in whom oral opioids are not suitable and whose analgesic requirements are unstable.

The GDG was uncertain of the cost implications of making this recommendation and, consequently, stated that the subcutaneous opioid with the lowest acquisition cost should be used.

3.6.6 Recommendations on first-line treatment if oral opioids are not suitable – subcutaneous delivery

Recommendation 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.

3.7 First-line treatment if oral opioids are not suitable – transdermal patch versus subcutaneous delivery

This topic looked at the clinical and cost effectiveness of transdermal patches versus subcutaneous opioids in patients with stable pain in whom oral opioids are not suitable.

3.7.1 Review question

- 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?

3.7.2 Evidence review

This review question focused on the effectiveness of the best transdermal patch available compared with the best subcutaneous opioid available 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. Papers were included if they compared the best transdermal patch (as determined by the evidence in section 3.5.2) with the best subcutaneous opioid (as determined by the evidence in section 3.6.2) in this patient group, in an RCT, or if they were systematic reviews of such trials. However, given that the search identified no papers comparing the relevant subcutaneous opioids, no such analyses could be undertaken in this question.

3.7.3 Evidence statements

No evidence was identified on the effectiveness of transdermal patch treatment compared with subcutaneous opioid treatment 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.

3.7.4 Health economic modelling

This topic was not considered a priority for health economic evaluation because of the limited data available. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.7.5 Evidence to recommendations

The aim of this topic was to compare transdermal patches with subcutaneous opioids for patients in whom oral opioids are not suitable and whose pain is stable. Given the lack of evidence on subcutaneous opioids, it was not possible to compare the clinical or cost effectiveness of transdermal patches and subcutaneous opioids.

However, the GDG agreed that subcutaneous opioids were likely to be more expensive than transdermal patches in the home setting, because of the need for nurse visits and the acquisition cost of the syringe driver. The GDG therefore agreed that transdermal patches would be the most appropriate

intervention for this group of patients. Since recommendation 1.1.11 already covers this clinical scenario, the GDG decided not to make any further recommendations.

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

Breakthrough pain can be defined as a transient exacerbation of severe pain over a background pain. These pains may be caused by actions of the patient such as movement or coughing but may fluctuate for no identifiable reason. Breakthrough pain should be distinguished from exacerbations of pain that are dose-related, such as pain occurring shortly before the next dose of analgesia is due. The treatment of breakthrough pain may require rescue doses of strong opioids.

This section only deals with people who can take oral opioids.

3.8.1 Review question

- 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)?

3.8.2 Evidence review

This review question focused on the effectiveness of immediate-release (IR) morphine compared with fast-acting fentanyls or IR oxycodone as treatment for breakthrough pain in patients with advanced and progressive disease who are currently being treated with strong opioids for background pain. Papers were included if they compared IR morphine with either IR oxycodone or fast-acting fentanyls in this patient group, in an RCT, or if they were systematic reviews of such trials. Table 12 lists the main characteristics of each of the included studies. For the review protocol and inclusion and exclusion criteria, and full list of excluded papers, see appendix D.

Although it was anticipated that meta-analyses would be conducted where possible, no such analyses were performed because it was not feasible given the body of evidence. Three studies were identified that compared IR

morphine with fast-acting fentanyls: one RCT (Davies et al. 2011) and two systematic reviews (Vissers et al. 2010; Zeppetella and Ribeiro 2006).

Immediate-release morphine compared with fast-acting fentanyls for breakthrough pain

Immediate-release morphine compared with fentanyl nasal spray for breakthrough pain

Davies et al. (2011) compared fentanyl pectin nasal spray (FPNS) with IR morphine sulphate capsules in patients with breakthrough cancer pain. In a per-episode analysis with clinically meaningful pain relief defined as a 2 or more point reduction in pain intensity, Davies et al. (2011) found that at 10 and 15 (but not at 5, 30, 45 and 60) minutes FPNS was associated with a 2 or more point reduction in pain intensity in a significantly higher proportion of breakthrough pain episodes than IR morphine, and at 15 and 30 (but not at 5, 10, 45 and 60) minutes FPNS was associated with pain relief of 2 or more points in a significantly higher proportion of breakthrough pain episodes than IR morphine. At 15, 30, 45 and 60 (but not 10) minutes, significantly more episodes achieved maximum total pain relief of 33% or more after FPNS compared with IR morphine. The percentage of episodes requiring rescue medication did not differ between FPNS and IR morphine, but patient satisfaction was superior for FPNS compared with IR morphine. Six FPNS and two IR morphine treatments (in eight patients) resulted in discontinuation of the study drug, and nasal tolerability did not differ between the treatments.

Vissers et al. (2010) conducted a systematic review of RCTs with a network meta-analysis that compared the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and IR morphine capsules for the treatment of breakthrough cancer pain (but only the results relevant to the questionnaire reported here). Six RCTs were included, four of which compared placebo with OTFC (Farrar et al. 1998, N = 92), INFS (Kress et al. 2009, N = 111), and FBT (Portenoy et al. 2006, N = 77; Slatkin et al. 2007, N = 86). The other two trials compared OTFC with IR morphine capsules (Coluzzi et al. 2001, N = 89 – also included in Zeppetella et al. 2009) and INFS with OTFC (Mercadante et al. 2009, N = 139). The network meta-

analysis showed that statistically significantly larger pain intensity differences were associated with INFS than IR morphine at 15, 30, 45 and 60 minutes.

Immediate-release morphine compared with oral transmucosal fentanyl for breakthrough pain

In a Cochrane review (without a meta-analysis) that aimed to determine the efficacy and adverse events of opioid analgesics (given by any route) used for the management of breakthrough pain in patients with cancer, Zeppetella and Ribeiro (2006) included four RCTs, three of which are not relevant to the present question. The fourth RCT compared OTFC with IR morphine (Coluzzi et al. 2001; N = 134, of whom N = 93 were randomised) and the results of this RCT are the only results that are reported from this Cochrane review. Coluzzi et al. (2001) found that OTFC was associated with superior pain relief and pain intensity difference at 15, 30, 45 and 60 minutes, and with global performance rating compared with IR morphine. OTFC was also associated with more than a 33% change in pain intensity at 15 minutes in significantly more pain episodes than IR morphine.

Immediate-release morphine compared with immediate-release oxycodone for breakthrough pain

No evidence was identified that compared IR morphine with IR oxycodone.

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Table 12 Summary of included studies comparing immediate-release morphine with fast-acting fentanyls or with immediate-release oxycodone for breakthrough pain

Author (year)	Study design	Population (N, inclusion criteria)	Treatment	Outcomes
Davies et al. (2011)	Multicentre, randomised, double-blind/double-dummy, cross-over study	N = 110 patients with a histologically confirmed diagnosis of cancer, who were receiving a fixed-schedule opioid regimen at a total daily dose ≥ 60 mg/day oral morphine for background cancer-related pain, and had 1–4 episodes/day of moderate-severe breakthrough pain	Fentanyl pectin nasal spray v immediate-release morphine sulphate capsules	Pain intensity at 5, 10, 15, 30, 45 and 60 minutes, pain relief at 5, 10, 15, 30, 45 and 60 minutes after dosing. Adverse events, nasal assessments, patient satisfaction
Vissers et al. (2010)	Systematic review with network meta-analysis	N = 6 RCTs on the management of breakthrough pain that allows comparison of intranasal fentanyl spray, fentanyl buccal tablet, oral transmucosal fentanyl nitrate and immediate-release morphine in adult cancer patients suffering from breakthrough pain and treated with opioid analgesics for the management of background pain reporting pain intensity difference	Intranasal fentanyl spray, fentanyl buccal tablet, oral transmucosal fentanyl nitrate v immediate-release morphine capsules, placebo	Pain intensity difference
Zeppetella and Ribeiro (2006)	Cochrane review without meta-analysis	N = 1 multicentre, randomised, double-blind/double-dummy, cross-over study with 93 randomised patients	Oral transmucosal fentanyl citrate v immediate-release morphine capsules	Pain relief, pain intensity difference
Abbreviations: RCT, randomised controlled trial; v, versus.				

Table 13 GRADE profile summary comparing fentanyl nasal spray with immediate-release morphine capsules for the treatment of breakthrough pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fentanyl nasal spray	Immediate-release morphine capsules	Relative (95% CI)	Absolute	
Pain at 15 and 30 minutes											
2[a]	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[b]	None	> 110[a]	> 100[a]	Not pooled. Favours fentanyl nasal spray		⊕⊕⊕O MODERATE
Pain at 45 and 60 minutes											
2[a]	Randomised trials	No serious limitations	Serious[c]	No serious indirectness	Serious[b]	None	> 110[a]	> 100[a]	Not pooled. See footnote c		⊕⊕OO LOW

[a] Two studies were included, one of which was a randomised cross-over trial with 110 patients (who are therefore counted in both treatment groups; Davies et al., 2011) and the other of which was a network meta-analysis with an overall total of six studies (none of which were direct trials; Vissers et al., 2010).

[b] Small N.

[c] Treatments differ in one, but not in the other study.

Abbreviations: CI, confidence interval.

Table 14 GRADE profile summary comparing oral transmucosal fentanyl with immediate-release morphine capsules for the treatment of breakthrough pain

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oral transmucosal fentanyl	Immediate-release morphine capsules	Relative (95% CI)	Absolute	
Pain at 15, 30, 45 and 60 minutes (pain intensity difference, pain relief)											
1[a]	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[b]	None	93[c]	93[c]	Favours oral transmucosal fentanyl		⊕⊕OO LOW

[a] Coluzzi et al. (2001) as reported in Zeppetella and Ribeiro (2006).

[b] Small N.

[c] The study was a cross-over trial so patients counted in both groups.

Abbreviations: CI, confidence interval.

3.8.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual 2009'.

Immediate-release morphine compared with fast-acting fentanyls for breakthrough pain

3.8.3.1 *Fentanyl nasal spray is associated with a better improvement in pain at 15 and 30 minutes (in two out of two studies; MODERATE QUALITY), but not at 45 and 60 minutes (in one out of two studies; LOW QUALITY) compared with immediate-release morphine capsules.*

3.8.3.2 *Oral transmucosal fentanyl is associated with a better improvement in pain at 15, 30, 45 and 60 minutes (in one out of one studies; LOW QUALITY) compared with immediate-release morphine capsules.*

Immediate-release morphine compared with immediate-release oxycodone for breakthrough pain

3.8.3.3 *No RCT evidence identified.*

3.8.4 Health economic modelling

This topic was considered a lower priority for health economic evaluation than the comparison of sustained-release preparations in maintenance treatment (see section 3.4.4). The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.8.5 Evidence to recommendations

The aim of this topic was to determine the most effective strong opioid treatment for breakthrough pain for those patients who are taking strong opioids for background pain, thereby improving their quality of life while avoiding adverse events or side effects. For this topic the GDG identified breakthrough and background pain, opioid side effects, adverse events, and health-related quality of life to be the most relevant outcomes.

No RCT evidence was found comparing immediate-release morphine with immediate-release oral oxycodone. However the GDG agreed, based on its

clinical experience, that oxycodone and morphine have very similar efficacies and side-effect profiles when used to manage breakthrough pain. However, morphine is significantly less expensive than oxycodone. Therefore, the GDG agreed to recommend that morphine is used for the first-line management of breakthrough pain.

For the comparison of immediate-release morphine with fast-acting fentanyls, evidence was reported for intranasal fentanyl compared with immediate-release morphine and for transmucosal fentanyl compared with immediate-release morphine. This evidence related only to breakthrough cancer pain. The GDG was aware that the available literature on non-cancer related breakthrough pain is consistent with results from the cancer population and therefore the GDG agreed it was appropriate to extrapolate this evidence to the wider population. No evidence was found for sublingual and buccal fentanyl (compared with immediate-release morphine). The overall quality of the evidence across each of these interventions ranged from low to moderate as assessed by GRADE.

Pain was the only outcome reported from the available evidence. No evidence was found for opioid side effects, adverse events, health-related quality of life or the percentage of patients switching opioid. Because the patients included in these trials were already on other opioids, it was difficult to attribute side effects to the opioids given for breakthrough pain.

Evidence reported in both systematic reviews and one RCT suggested that intranasal fentanyl was associated with superior pain relief at particular time points compared with immediate-release morphine. Although this difference was statistically significant differences were reported at only two out of six time points. At 10 minutes 52.4% of patients taking fentanyl had responded compared to 45% of patients taking morphine. At 15 minutes 75.5% of patients taking fentanyl had responded compared to 69.3% of patients taking morphine. The GDG did not think that these differences in pain relief from this single moderate quality trial were clinically relevant. The GDG was also aware of the relatively small population size in each of the included studies.

No formal cost-effectiveness analysis was conducted for this question and a systematic review of the economic literature yielded no relevant data. The cost of treating an average breakthrough event was calculated, as shown in table 15. For the purpose of the costing exercise, it is assumed that the dose of the immediate-release preparations is equal to one-sixth of the regular daily dose. The GDG noted that fast-acting fentanyls (especially those which also require a spray canister) are considerably more expensive than immediate-release morphine.

Table 15 Costs of breakthrough pain medication

Therapy	Regular dose	Breakthrough dose[a]	Average price per breakthrough event
Morphine	60 mg	10 mg	£0.09
Oxycodone	30 mg	5 mg	£0.20
Fentanyl	25 µg/h[b]		
Intranasal[c]		100 µg	£4.88
Sublingual		100 µg	£4.99
Buccal		100 µg[d]	£4.99
Buccal		200 µg[e]	£5.85

[a] Typically one-sixth of regular daily dose.
[b] Patch dose.[c] Average of Instanyl (100 µg) and PecFent (100 µg).
[d] Initial dose of Effentora (100 µg).
[e] Initial doses of Actiq (200 µg).

The GDG was satisfied that there was limited evidence to suggest that fentanyl is more clinically effective than immediate-release morphine (and immediate-release oxycodone) for the management of breakthrough pain. However, it felt the cost impact of recommending fentanyl over immediate-release morphine or oxycodone would be considerable and therefore could not be justified. Therefore, the GDG agreed to recommend that fast-acting fentanyls are not offered.

3.8.6 Recommendations on breakthrough pain

Recommendation 1.1.14

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

Recommendation 1.1.15

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

Recommendation 1.1.16

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

3.9 Management of constipation

Constipation is common in patients receiving palliative care for advanced and progressive disease. It may be associated with other factors such as flatulence, bloating, or a sensation of incomplete evacuation. Opioids can cause constipation by different mechanisms: they decrease muscular propulsive intestinal activity, increase non-propulsive activity and enhance the absorption of fluid and electrolytes from the bowel lumen. Although general principles for avoiding constipation should be followed, patients taking opioids will often need pharmacological intervention in the form of one or several laxatives. They may need to be admitted to hospital or hospice because further investigation and more interventional management (for instance, regular enemas) often cannot be undertaken at home. Complications of constipation can include pain, overflow diarrhoea, bowel obstruction and urinary retention.

Some opioids are thought to be more constipating than others (see section 3.4.2). The GDG wanted to investigate the evidence on whether laxative treatment or switching the type of opioid medication would be a more effective intervention in reducing constipation for patients with troublesome constipation on opioids.

The GDG felt that adherence to laxative treatment was important. It was felt that a significant proportion of patients in primary and secondary care did not take laxatives regularly, if at all.

3.9.1 Review question

- 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?

3.9.2 Evidence review

This review question focused on the effectiveness of laxatives for the treatment of constipation resulting from strong opioids taken for pain by

patients with advanced and progressive disease. Papers were included if they compared laxative treatment with or without an associated switch in opioid in patients experiencing constipation from strong opioid treatment, in RCTs, or if they were systematic reviews of such trials:

However, the search identified no such papers.

3.9.3 Evidence statements

3.9.3.1 No evidence was identified on the effectiveness of laxative treatment with or without opioid switching in patients experiencing constipation as a side effect of strong opioid treatment.

3.9.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.9.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing constipation as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to be the most important outcomes. The GDG wanted to investigate the management of constipation by comparing the use of laxatives with switching opioid. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that, despite the lack of evidence, recommendations were required on managing these common side effects in order to improve patient care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG considered constipation to be a side effect that will affect nearly all patients taking strong opioid treatment and that this side effect will persist

unless treated. The GDG therefore agreed that the best treatment would be to start laxatives when starting opioid treatment, and that laxative treatment should be optimised before switching opioids. However, given the lack of evidence, the GDG did not feel able to recommend a specific laxative or class of laxatives. The GDG was also aware that patients often do not understand that laxatives need to be taken regularly at the required dose to help with constipation or that laxatives take time to have an effect on constipation. It therefore recommended that patients be informed about these issues.

3.9.6 Recommendations on managing constipation

Recommendation 1.1.17

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

Recommendation 1.1.18

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

Recommendation 1.1.19

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

Recommendation 1.1.20

Optimise laxative treatment for the management of constipation before considering switching strong opioids.

3.10 Management of nausea

Nausea is defined as the unpleasant feeling of the need to vomit, often accompanied by autonomic symptoms. Opioids commonly cause nausea by several mechanisms: gastroparesis, constipation or through central effects on the brain. Prevalence rates of nausea in cancer patients taking opioids can be up to 40%.

For patients nearing the end of life, nausea causes significant psychological distress and can lead to reduced quality of life. Hospital and hospice admissions may be necessary to control symptoms, and parenteral rather than oral treatment regimens may have to be started.

For patients who need opioids, nausea and vomiting are dose-limiting adverse effects, and therefore their management can be seen as a prerequisite for effective pain management. Strategies to avoid nausea and vomiting when opioid treatment begins include prescribing a regular anti-emetic agent alongside the opioid. Strategies to address established nausea and vomiting in patients already taking opioids include anti-emetic medication, stopping or reducing opioids (including using non-opioid co-analgesics for 'opioid-sparing'), switching the opioid and changing the route of administration of the opioid.

The GDG rated the importance of this adverse effect as high, and felt that management of this common problem was inconsistent in both primary and secondary care settings. Potential sequelae of this common problem were felt to have a large effect on patients' quality of life and the involvement of healthcare providers.

3.10.1 **Review question**

- 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?

3.10.2 Evidence review

This review question focused on the effectiveness of anti-emetics for the treatment of nausea resulting from strong opioids taken for pain by patients with advanced and progressive disease. Papers were included if they compared anti-emetic treatment with or without an associated switch in opioid in patients experiencing nausea from strong opioid treatment, in RCTs, or if they were systematic reviews of such trials:

However, the search identified no such papers.

3.10.3 Evidence statements

3.10.3.1 No evidence was identified on the effectiveness of anti-emetic treatment with or without opioid switching in patients experiencing nausea as a side effect of strong opioid treatment.

3.10.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.10.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing nausea as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to be the most important outcomes. The GDG wanted to investigate the management of nausea by comparing the use of anti-emetics with switching opioid. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that despite the lack of evidence, recommendations were required on managing these common side effects in order to improve patient

care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG noted that nausea tends to occur when starting strong opioid treatment or when increasing the dose of an opioid. In such cases, the nausea is normally transient and resolves without the need for medical intervention. However, many patients are not aware of this and may stop taking the opioid if they experience nausea. The GDG therefore agreed to make a recommendation that would raise patients' awareness about this.

The GDG was also aware that opinion is divided about prescription of routine anti-emetic treatment when starting or titrating opioids. Given the lack of evidence in this area, the GDG did not feel it was possible to make a definitive recommendation on this issue and so decided to recommend further research. The GDG agreed that if nausea is persistent and does not respond to anti-emetic treatment, switching opioids should be considered.

3.10.6 Recommendations and research recommendations on managing nausea

Recommendation 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.

Recommendation 1.1.22

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

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B2

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.

3.11 Management of drowsiness

Drowsiness is a common and sometimes serious adverse effect of opioid treatment in patients with advanced and progressive disease. The GDG defined drowsiness as a decreased level of consciousness characterised by sleepiness and difficulty in remaining alert but with easy arousal by stimuli. The degree of sedation in patients taking opioids can vary from mild sleepiness and fatigue to severe drowsiness or coma, and may be accompanied by other central nervous system side effects, such as hallucinations, cognitive impairment, agitation, myoclonus, respiratory depression and delirium.

The GDG felt that one of the most common problems encountered in the initial prescribing of opioids was drowsiness, and that it needed to be addressed. The question the group decided to focus on was whether opioid dose reduction or switching opioids would be more effective in reducing drowsiness.

Equivalent opioid dosage is calculated using conversion charts, and practice can vary regionally. This is further complicated by the fact that opioid dosage-equivalence can vary among individuals.

3.11.1 **Review question**

- 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?

3.11.2 **Evidence review**

This review question focused on the effectiveness of opioid switching and opioid dose reductions for the treatment of drowsiness resulting from strong opioids taken for pain by patients with advanced and progressive disease. Papers were included if they compared opioid dose reductions with opioid switching in patients experiencing drowsiness from strong opioid treatment in RCTs, or if they were systematic reviews of such trials.

However, the search identified no such papers.

3.11.3 Evidence statements

3.11.3.1 No evidence was identified on the effectiveness of dose reduction compared with opioid switching in patients experiencing drowsiness as a side effect of strong opioid treatment.

3.11.4 Health economic modelling

This topic was not considered a priority for health economic analysis because of the relative low cost impact and the lack of available data. The cost-effectiveness literature on this topic was reviewed but no evidence was found.

3.11.5 Evidence to recommendations

The aim of this topic was to determine the most effective management strategy for patients experiencing drowsiness as a result of strong opioid treatment.

The GDG considered the management of common opioid side effects, and the impact that management of these has on treatment adherence and pain control, to be the most important outcomes. The GDG wanted to compare dose reduction with switching opioid for managing drowsiness. However, no randomised trials were identified that looked at the interventions of interest.

The GDG noted that, despite the lack of evidence, recommendations were required on managing this common side effect in order to improve patient care. The group therefore agreed to make recommendations based on its clinical experience.

The GDG noted that a significant proportion of patients taking strong opioids experience central side effects, such as drowsiness. The GDG was aware that if these side effects are experienced when starting strong opioid treatment or when doses of opioids are increased, they may be transient and may not require medical intervention to resolve. Therefore, the GDG decided to recommend that patients are informed of this.

However, the GDG agreed, based on its clinical experience, that if central side effects persist or are more severe, treatment by either opioid switching (if pain

is not controlled) or dose reduction (if pain is controlled) is needed. The GDG also agreed that further research was needed to investigate the impact of early switching compared with dose reduction in patients experiencing persistent or severe central side effects because this has not been formally evaluated.

The GDG also agreed that when starting opioid treatment or at dose increase, patients may have impaired concentration which could affect their ability to undertake manual tasks such as driving. Since current formal guidance on whether patients should drive while taking opioids is unclear, and this query is frequently raised by patients, the GDG decided to recommend that potential impairment in relation to driving should always be discussed with the patient.

3.11.6 Recommendations and research recommendations on managing drowsiness

Recommendation 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[4] and undertake other manual tasks.

Recommendation 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.

Recommendation 1.1.25

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

[4] http://www.dft.gov.uk/dvla/medical/ataglance.aspx

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B3

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.

4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG[xxx])'. Note: these details will apply when the guideline is published.

6 Other versions of this guideline

6.1 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from http://pathways.nice.org.uk/pathways/[xxx]

Note: these details will apply when the guideline is published.

6.2 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG[xxx]/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N[xxxx]). Note: these details will apply when the guideline is published.

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about strong opioids in advanced and progressive disease.

7 Related NICE guidance

Published

- Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline 96 (2010). Available from www.nice.org.uk/guidance/CG96
- Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Low back pain: early management of persistent non-specific low back pain. NICE clinical guideline 88 (2009). Available from www.nice.org.uk/guidance/CG88
- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79
- Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal 159 (2008). Available from www.nice.org.uk/guidance/TA159
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- Osteoarthritis: the care and management of osteoarthritis in adults. NICE clinical guideline 59 (2008). Available from www.nice.org.uk/guidance/CG59
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGSP

8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

9 References

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10 Glossary and abbreviations

10.1 Glossary

Adverse effects

Harmful or undesirable effects of an intervention.

Anti-emetic

A drug taken to prevent or treat nausea or vomiting.

Bioavailability

The amount of or rate at which a substance or drug is pharmaceutically available to, or active in, the body.

Background pain

Chronic persistent pain.

Breakthrough pain

A transient increase in pain intensity over background pain, typically of rapid onset and intensity, and generally self-limiting with an average duration of 30 minutes.

Concomitant medicine

Drugs that are given either at the same time or almost at the same time

Formulation

The process in which different chemical substances, including the active drug, are combined to produce a final medicinal product.

Health economic model

Mathematical and statistical techniques are used to synthesise the relevant costs and outcomes for part of a clinical pathway or a whole clinical pathway. Like most models, they typically represent a simplified view of reality. They are useful tools for decision makers who need to consider the costs and

benefits associated with alternative courses of action. In particular, they are useful when decisions about the cost effectiveness of care depend on the effectiveness of multiple combinations of healthcare options (tests, treatment, long-term follow-up).

Immediate-release

A dosage form that is intended to release all the active ingredient on administration with no enhanced, delayed or extended release effect.

Imprecision

The results of quantitative studies with small samples and few events (and therefore wide confidence intervals) are imprecise.

Incremental cost-effectiveness ratio

The difference in the mean costs in the population of interest divided by the difference in the mean outcomes in the population of interest when comparing two interventions.

Indirectness

A type of comparison that may be carried out when a comparison of intervention A versus B is not available, but A was compared with C and B was compared with C. Such studies allow indirect comparisons of the magnitude of effect of A versus B.

Life year

A measure of health outcome that shows the number of years of remaining life expectancy.

Maintenance treatment

The various kinds of treatment (usually medical) given to patients to enable them to maintain their health in a disease-free, or limited-disease, state.

Network meta-analysis

A type of meta-analysis that takes into account both direct and indirect comparisons between interventions of interest (see also **Indirectness**).

Open-label

A term used to describe the situation when both the researcher and the participant in a research study know the treatment the participant is receiving. Open-label is the opposite of double-blind when neither the researcher nor the participant knows what treatment the participant is receiving.

Opioid

A chemical substance that has a morphine-like action in the body. The main purpose of use is for pain relief.

Palliative care

The active holistic care of patients with advanced, progressive illness; that is, the management of pain and other symptoms, and the provision of psychological, social and spiritual support. The goal of palliative care is achievement of the best quality of life for patients and families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.

Pharmacokinetics

The process by which a drug is absorbed, distributed, metabolised and eliminated by the body.

Preparation

A final pharmaceutical product which contains an active drug plus the added ingredients such as stabilisers, flavourings or coatings to enable the drug and dose to be delivered in an accurate and replicable way as stated in the Summary of Product Characteristics.

Rescue dose

The dose of an analgesic required for the relief of **breakthrough pain**.

Sensitivity analyses

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. The different types of sensitivity analysis are:

• One-way sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequence of each parameter on the results of the study.

• Multi-way sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

• Threshold sensitivity analysis: the critical values of parameters above or below which the conclusions of the study will change are identified.

• Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques.

Stable pain

Pain that is predictable in its pattern and intensity, and which requires regular analgesia that can be planned in a non-urgent context.

Strong opioid

Morphine-like drugs (eg diamorphine, fentanyl, oxycodone, buprenorphine). Codeine and dihydrocodeine are weak opioids.

Subcutaneous injections

A subcutaneous injection is given in the fatty layer of tissue just under the skin.

Sublingual

Underneath the tongue.

Sustained-release

Designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimal side effects.

Transdermal patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Transient

For a short time only; of short duration; temporary or transitory.

Titration

Incremental increase in drug dosage to a level that provides the optimal therapeutic effect.

Toxicity

The degree to which a substance can harm humans or animals.

Unstable pain

Pain that is unpredictable in its pattern and intensity, and which requires irregular analgesia in an urgent context.

Please see the NICE glossary (www.nice.org.uk/website/glossary/glossary.jsp) for an explanation of terms not described above.

10.2 Abbreviations

Abbreviation	Term
BNF	British National Formulary
CI	Confidence interval
EAPC	European Association for Palliative Care
FBT	Fentanyl buccal tablet
FPNS	Fentanyl pectin nasal spray
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HE	Health economics
ICER	Incremental cost-effectiveness ratio
INFS	Intranasal fentanyl spray
IR	Immediate release
OTFC	Oral transmucosal fentanyl citrate
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
RCT	Randomised control trial
QALD	Quality-adjusted life days
QALY	Quality-adjusted life years
QoL	Quality of life
SR	Sustained release
SIGN	Scottish Intercollegiate Guideline Network

Appendix A Contributors and declarations of interests

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The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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Declarations of interests

Dr Damien Longson (Chair): No interests declared.

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Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B1 Communication

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?

Why this is important

We know from qualitative work that patients do not always understand how to take strong opioids or the difference between sustained-release and rescue medication. Patients, their carers and some clinicians fear the adverse effects of these drugs and believe that strong opioids, especially morphine, can be negatively associated with adverse effects and death. To improve adherence and to enable patients and carers to benefit from the proven analgesic effects of strong opioids, research should be undertaken to determine how to address the main concerns of patients, the level of information they require and the best time and methods to deliver this. The benefits of greater involvement in this process by specialist nurses or pharmacists should also be examined in research.

B2 Side effects

Is prophylactic prescription of anti-emetic treatment or 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.

Why this is important

Patients may experience transient nausea when starting opioid treatment and opioid-induced nausea often responds to anti-emetic treatment. When nausea occurs, timely review by a healthcare professional to start anti-emetic treatment can be difficult to achieve in the community setting. Prescription of routine anti-emetic treatment when starting opioids is controversial. It is important to evaluate the positive and negative impact of this strategy; while it may reduce opioid-induced nausea, improve adherence with opioid treatment, and reduce use of healthcare resources, the added burden to the patient and overall cost effectiveness are currently unclear.

B3 Side effects

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.

Why this is important

The common gastrointestinal opioid-induced side effects such as constipation or nausea can often be managed with concomitant medications. A significant proportion of patients starting strong opioids experience central side effects that patients report as distressing and often limit daily activities. Although central side effects may be transient, persistent symptoms can be difficult to treat and cause significant morbidity. The clinical strategy of opioid switching has been shown to reduce central side effects. The impact of early switching, rather than dose reduction or a ‘watch and wait’ strategy has not been formally evaluated but may improve both time to opioid response and health-related quality of life.

Appendix C Guideline scope

See separate file.

Appendix D How this guideline was developed

See separate file.

Appendix E Evidence tables

See separate file.

Appendix F Full health economic report

See separate file.