Review

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Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: An EPCRC opioid guidelines project

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Abstract
The European Palliative Care Research Collaboration is updating the EAPC recommendations on opioids in cancer pain management. A systematic literature search on Medline on the use of alternative routes for opioid application identified 242 papers, with 72 publications included in the final evaluation. Two or more alternative routes of opioid application were compared in 18 papers with a total of 674 patients. The best evidence base was available for the subcutaneous route. A comparison of subcutaneous and intravenous routes found no differences, confirming both routes as feasible, effective and safe. Efficacy and safety of the rectal route was comparable to the parenteral route. The side effect profile seemed to be very similar for the subcutaneous, intravenous, rectal or transdermal routes. Local side effects were reported for rectal application as well as for subcutaneous and transdermal administration. In conclusion, the systematic review found good evidence that subcutaneous administration of morphine or other opioids is an effective alternative for cancer patients if oral treatment is not possible. However, for a number of patients intravenous, rectal or transdermal therapy will offer a good alternative to the subcutaneous route. The review found no significant differences in efficacy or side effects between the alternative application routes.

Keywords
Neoplasm, pain, opioids

Background

Oral opioids have been recommended as the mainstay of cancer pain management, most prominently in the recommendations of the World Health Organization.[1–3] The recommendations of the European Association for Palliative Care (EAPC) on the use of morphine and other opioids in 2001 also considered oral opioids as the first-line approach to cancer pain.[4]

However, if patients are unable to take opioids orally the recommendations listed subcutaneous application as the preferred alternative, as it is simpler and less painful than intramuscular injections. This was graded as a rather weak recommendation, based on expert opinion rather than on controlled trials. The recommendations also suggested that opioids other than morphine such as diamorphine or hydromorphone may be preferred for parenteral administration, as they are more soluble than morphine and thus smaller injection volumes are necessary. However, this would be subject to availability, which differs in the European countries. Transdermal application also was listed as an alternative in the recommendations, if patients have stable opioid dose requirements, and rectal application for those patients who prefer that route.

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Subcutaneous injection would result in a more rapid onset of analgesia than oral administration, with peak plasma concentrations achieved within 15–30 minutes. Owing to the low bioavailability with oral administration of morphine, the conversion ratio of oral to subcutaneous or to intravenous application was estimated in the recommendations as between 2 : 1 and 3 : 1. However, this also was graded as a weak recommendation, with no published research to support it. The recommendations stated that the relative potency ratio of oral to parenteral morphine has been highly controversial, and seems to vary considerably not only interindividually, but also according to the circumstances in which the opioid is used.

For continuous parenteral application subcutaneous infusion was recommended, preferably with portable syringe driver pumps. Intravenous opioid infusion was named as an alternative for patients who already have an indwelling intravenous line, and transdermal opioid therapy could be a useful non-invasive alternative. Again this recommendation was graded as weak.

Buccal, sublingual and nebulized routes of administration of morphine were not recommended because at that time there was no evidence of clinical advantage over the conventional routes. However, sublingual buprenorphine was recommended as a useful alternative to low-dose oral morphine for patients who have difficulty in swallowing.

Surveys on clinical practice have shown that physicians often prefer other strategies. In a US study the percentage of patients on intravenous opioid therapy was increased from 33% to 55% after admission to the cancer pain service.[5] However, until the time of discharge 57% of patients received opioids via the oral route, 18% intravenous, but also 18% transdermal and 5% subcutaneous application. Convenience, but also non-invasiveness, the need for rapid effect, impaired gastrointestinal function and intolerance of oral opioids were named as reasons for the preference of a specific route. More recently, a telephone survey on medication kits for managing symptomatic emergencies in the home found oral, sublingual and rectal routes of administration as common.[6] However, these preferences may have been due to the setting of emergency interventions by hospice nurses, but not by physicians.

A Japanese survey[7] found that physicians used the oral route most frequently for patients receiving home care and requiring morphine, with the rectal route being second in frequency. Rectal application was prescribed by more than 80% of the physicians in this survey, whereas subcutaneous application was used by only 44% and intravenous by 4%. Hospital-based physicians used the subcutaneous route much more frequently than physicians working at clinics.

From Europe, an older Swedish nationwide survey reported a preference of intermittent subcutaneous or intramuscular injections of morphine and less frequent use of continuous intravenous or subcutaneous infusions or intermittent injections via an indwelling butterfly needle.[8] A recent German survey from a Berlin home care service explained that in the last days of life 45% of the patients were treated with subcutaneous injections or infusions.[9] Intravenous opioid application was performed in 13% of the patients, and the rest of the patients were divided evenly between oral and transdermal opioid administration. However, reasons for specific preferences for any routes were not provided. An Italian survey on all opioid prescriptions for cancer patients in the Venetian region found only 21% of all patients dying from cancer had been prescribed opioids.[10] From these patients 64% were treated with oral morphine, 5% with injectable morphine, 23% with transdermal fentanyl and 8% with sublingual buprenorphine.

Considering the survey results from clinical practice and the introduction of new therapeutic systems with opioids such as new patch systems or intranasal sprays with fentanyl it seems necessary to update the EAPC recommendations.[11] The revision of the recommendations will be based on systematic reviews to provide high-level evidence-based guidelines. This guideline work is part of the European Palliative Care Research Collaborative (EPCRC), an international collaborative aiming to produce clinical guidelines on pain, depression and cachexia.[12]

For this review, the use of alternative routes for opioid application if patients are unable to take morphine orally are evaluated for efficacy and safety in a systematic literature review. An overlap with the reviews of transdermal fentanyl and transdermal buprenorphine, with review the on breakthrough pain as well as with the review on equianalgesic dose ratios is to be expected. This review focuses on studies where two or more application routes are compared, preferably with the same opioid used for both routes.

Methods

This review is part of a series of literature reviews that will be used to revise the guidelines of the EAPC on opioid management in cancer pain and followed the protocol provided for this series (see http://www.epcrc.org). The remit for this review asked for the evaluation of alternative routes for opioid application in adult patients with moderate to severe pain directly due to cancer, and who are unable to take oral opioids. The evaluation should investigate whether there is any evidence to support the use of one alternative route (transdermal, parenteral, rectal, subcutaneous,

intravenous, oral transmucosal and nasal) over another in the management of pain.

We performed a systematic literature review in Medline (PubMed) with a search strategy that was coordinated with that provided in the series protocol and with those of other reviews in the guideline revision. In correlation with the template the search was restricted to publication in English language and to the time period from 1966 to July 2009. The search template was modified to retrieve only publications that included two alternative routes (Table 1). The comparisons covered by the search strategy are shown in Table 2.

Eligibility for assessment was performed by one of the authors (LR). Publications were excluded if they reported on animals, on children or on non-cancer patients. Studies testing drugs other than opioids were also excluded, as were studies on postoperative pain, even if they had recruited cancer patients. Breakthrough pain is a subject for a separate systematic review, so these studies were considered for inclusion only if they described treatment of pain exacerbations or tried to influence baseline pain levels as well. Non-systematic reviews were also excluded. Surveys on clinical practice, for example as a questionnaire survey on the use of subcutaneous infusions, were also excluded.

Studies were included if they allowed for a comparison of two different application routes, either from switching routes or from different cohorts of patients. Individual case reports and case series were considered only for evaluation of safety and toxicity, but not for evaluation of efficacy. Studies on pharmacokinetics or reports on plasma concentrations were not considered, if they did not include clinical data on efficacy or safety.

Table 1. Search strategy for Medline

Search	Queries	Result
#9	Search #7 AND #8 Limits: Publication Date from 1966 to 2009/07/30, English	242
#8	Search morphine OR hydromorphone OR oxycodone OR fentanyl OR buprenorphine OR methadone OR polamidon* OR Levomethadone OR palladon OR oxycodon OR durogesic OR transtec OR actiq OR effentora OR temgesic OR dilaudid OR instanyl OR abstral Limits: Publication Date from 1966 to 2009/07/30, English	60,471
#7	Search #4 AND #5 Limits: Publication Date from 1966 to 2009/07/30, English	513
#6	Search #4 AND #5	608
#5	Search (subcutaneous* AND intravenous*) OR (intravenous* AND transdermal) OR (subcutaneous* AND transdermal) OR ((transmucosal OR buccal OR sublingual) AND (transdermal OR subcutaneous* OR intravenous* OR parenteral OR intranasal OR rectal)) OR (intranasal* AND (transdermal OR subcutaneous* OR intravenous* OR parenteral OR rectal)) OR (rectal AND (transdermal OR subcutaneous* OR intravenous* OR parenteral)) OR (parenteral AND (transdermal OR subcutaneous* OR intravenous*))	37,859
#4	Search (#1 OR #2) AND #3	64,865
#3	Search pain	414,626
#2	Search cancer OR neoplasm OR tumour OR oncol* OR carcinoma* OR malignan*	26,18,090
#1	Search palliative care OR hospice OR terminal care OR terminally ill	71,909

Table 2. Comparison of application routes (white boxes indicate the comparisons of alternative application routes that were included in the literature search strategy)

	Transdermal	Subcutaneous	Intravenous	Oral transmucosal	Intranasal	Rectal
Transdermal						
Subcutaneous						
Intravenous						
Oral transmucosal						
Intranasal						
Rectal						
Parenteral						

Information on analgesic effectiveness and on safety was extracted from the studies and entered into a spreadsheet. The data record form included trial design, patient number and diagnoses, opioid and application route, indicators on effectiveness and safety as well as the results reported for these parameters. The data record form was based on the template provided in the review series.

Sources of bias were collected and provided as notes in the data form. Bias was not assessed systematically, as the review included not only randomized, but also non-randomized controlled trials. The review also did not investigate the risk of bias across studies.

Meta-analysis was not planned for this review, as a scoping review had shown that the differences in the outcome indicators used in the studies would prevent a meaningful compilation of results. Moreover, with the number of comparisons required, the number of controlled studies available for each comparison was expected to be small.

Results

The search strategy retrieved 242 studies. Excluding publications on paediatric palliative care or on non-cancer patients, in animals or testing drugs other than opioids or publications on pharmacokinetics that did not report data on efficacy or safety left 72 studies. These were evaluated in more detail. Eighteen of these studies including a total of 674 patients compared two or more alternative routes of opioids application (Figure 1). Intravenous or subcutaneous application was more frequently one comparator than other alternative routes of administration. In addition to these studies three systematic review included results that were relevant for this review.[13–15]

Subcutaneous route

A recent systematic review[13] evaluated Medline publications for the time period of 1975 to 2002. Two retrospective surveys with 82 patients[16,17] and 9 prospective trials with a total of 244 patients,[18–26] 8 of them controlled trials, using either crossover or parallel group design. One of these studies compared subcutaneous application of fentanyl with that of morphine,[18] another one hydromorphone and morphine.[20] No differences in efficacy were reported in these two trials. Two trials with morphine[19,21] and one with hydromorphone[25] compare subcutaneous with other parenteral or spinal application routes. Three trials evaluate different application regimes such as patient-controlled with continuous infusion.[22–24] Again no differences are described. One observational study confirmed the feasibility of the subcutaneous route even for extended periods.[26]

Similarly, the Cochrane review on hydromorphone by Quigley[14] included 12 studies in chronic pain, and five of these studies with a total of 177 patients used alternative routes. The author reported no difference between subcutaneous and intravenous route in one study,[25] between continuous infusion or

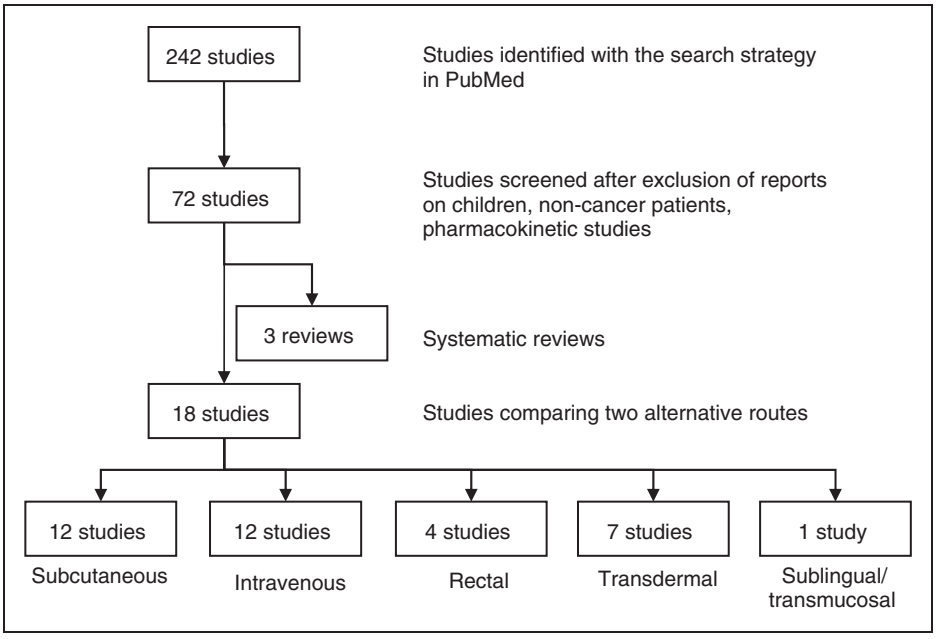

Figure 1. Flowchart for the literature review (multiple entries).

patient-controlled analgesia via the subcutaneous route in two studies[22,23] or between subcutaneous infusions with morphine or hydromorphone.[20] The fifth study compared intramuscular application of hydromorphone with morphine,[27] again with no differences between drugs.

In our systematic review the search strategy identified 11 studies with 466 patients which compared different application routes (Table 3). Four of the these studies compared subcutaneous with intravenous application,[25,28–30] in three studies with morphine, in the other with hydromorphone. In the study of Moulin et al.,[25] a 48-hour infusion with hydromorphone was tested in a controlled crossover comparison, finding no difference in efficacy or side effects. Elsner et al.[28] compared both routes for opioid titration for severe pain exacerbations, finding similar efficacy and only a tendency for faster onset with intravenous titration. In this study (as well as in the others) the small sample size with $n = 39$ could have masked significant differences, as the power analysis showed that a sample size of $n = 80$ would have resulted in significance of the difference. Drexel[29] combined results from two small studies in their report, with a change from subcutaneous application to intravenous in one study and from intravenous to subcutaneous in the other. No differences were found for pain relief, quality of life or side effects. Koshy et al.[30] compared two groups of patients receiving either subcutaneous or intravenous infusions in a resource poor setting, and reported no differences in efficacy or safety, even if no pump systems were used.

The study of Bruera et al.[31] used a crossover method to compare rectal application of morphine with the subcutaneous route. With an equianalgesic ratio of 2.4:1 (rectal:subcutaneous) similar efficacy and side effects were reported for both routes, and the authors concluded that the rectal application is a reliable and non-invasive alternative for patients who are not able to take oral medications. In a second study from the same group patients who were treated with subcutaneous application of hydromorphone were switched either to oral or rectal methadone.[32] In this study the switch to rectal application of methadone was twice as fast as the oral route.

The other six studies used a sequential switch from intravenous application to subcutaneous[21,33,34] or from transdermal to subcutaneous.[17,35,36] In the latter three studies fentanyl, sufentanil, diamorphine and hydromorphone were used for subcutaneous application. All studies reported good analgesic efficacy with subcutaneous application. The study of Walsh et al.[34] found better pain relief in patients switched from intravenous to oral application than in those switched from intravenous to subcutaneous, but this may have been related to different indications for these switches, as the study described prescribing patterns and did not use a controlled methodology. In a retrospective evaluation of patients on the Liverpool Care Pathway of the Dying matched pairs were built for patients on transdermal fentanyl and those on subcutaneous diamorphine.[36] The authors found no significant differences between groups, and good pain control in both. In all studies local toxicity at the needle insertion site was documented only in a few cases. The incidence of systematic side effects was comparable between intravenous and subcutaneous application[21] and symptom control was considerably improved after patients were switched over to subcutaneous from oral or transdermal pretreatment.[35]

Another 24 studies including 1102 patients were identified that reported on subcutaneous application of opioids, using a wide range of opioids such as morphine, oxycodone, hydromorphone, diamorphine, fentanyl, sufentanil, methadone or ketobemidone. Local toxicity at the needle insertion site was reported infrequently with erythema, swelling, bleeding and subcutaneous plaques. Systematic side effects were as expected with opioid treatment, most often with constipation, nausea and drowsiness.

In the studies comparing intravenous with subcutaneous application of the same opioid, analgesic effective doses were similar for both routes. Conversion factors have been described in some studies, but mostly only calculated from small numbers of patients and often with a wide range and differences in different studies. For subcutaneous morphine to oxycodone a conversion factor of 1.2 ± 0.4 and for subcutaneous hydromorphone to oxycodone 0.5 ± 0.4).[37] These conversion factors are slightly different from the equivalent conversion factors of the oral application of the same opioids. In another study the conversion factor was described as 1.2 ± 1.3 for subcutaneous hydromorphone to oral methadone and 3 ± 2 for subcutaneous hydromorphone to rectal methadone.[32] This is different to the conversion factor of subcutaneous hydromorphone to oral methadone of 0.93, and of subcutaneous hydromorphone to rectal methadone of 0.53 found in another study.[38]

Intravenous route

In the Cochrane review on hydromorphone by Quigley[14] only one of 12 studies in chronic pain used the intravenous route. In this study the authors reported no difference between subcutaneous and intravenous route.[25]

The literature search identified 12 studies with 296 patients comparing intravenous with other routes of application (Table 4). Seven of these studies[21,25,28–30,33,34] compared intravenous with

Table 3. Studies comparing subcutaneous with other application routes

First author, year	Study design	Patients			Results: efficacy		Results: side effects			
		Patient numbers	Route	Drugs	Outcomea measures	Summary of results	Outcome measures	Summary of results	Narrative summary of results	Notes
Anderson 2004	Systemic review	9 studies (326 patients)	sc	Morphine, hydromorphone, fentanyl	Miscellaneous	Continuous sc infusion is efficient	Miscella neous	Continuous sc infusion is safe	Medline research 1975–2002, 9 prospective and 2 retrospective studies, continuous sc infusion is safe and effective, no major differences between opioids or application regimens	Limited to English language and human
Quigley 2002	Systemic review	5 studies (177 patients)	sc, iv, im	Hydromorph one, morphine	Miscellaneous	No difference between routes or application mode	Not reported	Not reported	Search until November 2006, 12 studies on chronic pain, 5 with alternative routes, no difference reported for one study comparing iv versus sc, 2 studies comparing patients-controlled application versus continuous infusion or 2 studies comparing hydromorphone with morphine (one study im, one study sc)	
Elsner 2005	Controlled cohort study, randomized	39	iv (21 patients) versus sc (18)	Morphine	VAS pain intensity (0= no pain, 10= worst pain), VRS pain intensity (no, slight, moderate, severe, very severe, unbearable pain), %TOTPAR	%TOTPAR 31% (iv) 15% (sc), VAS pain intensity reduced from 83±17 to 32±23 (iv) and from 68±24 to 42±27 (sc)	Not reported	Not reported	Titration doses 4-34 mg (iv) and 10-200 mg (sc). No significant difference in mean time to reach adequate analgesia with 53 minutes (iv) and 77 minutes (sc). Adaptation of continuous opioid dosage following titration and calculation of conversion factor in 10 patients (iv) and 8 patients (sc): conversion factor 6.6±7.9 (iv) and 3.7±3.3 (sc). Both routes are adequate to antagonize pain exacerbations quickly and adapt the dosage of continuous medication.	Power analysis reported, for faster onset 2x40 patients would have been needed, for %TOTPAR power was 0.81

(continued)

Table 3. Continued

First author, year	Study design	Patients			Results: efficacy		Results: side effects			
		Patient numbers	Route	Drugs	Outcomea measures	Summary of results	Outcome measures	Summary of results	Narrative summary of results	Notes
Drexel 1991	Crossover non-randomized controlled study	15	sc versus iv	Morphine	Pain score, quality of life score, no details on scores reported	Morphine dosage identical for sc and iv route, (73±41 mg/d), pain 2.2 ±1.1 for sc, 2.1±1.1 for iv, quality of life index 2.9±2.3 for sc, 3.1±2.3 for iv	No information	No difference in side effects	8 patients with iv-infusion (crossed over to sc-pump), 7 patients with sc-pump (crossed over to iv-infusions). So in all 15 patients at least 72 h of iv-infusion compared to 2-20 weeks of sc-pump. No difference was found in pain relief, quality of life or side effects	Combination of data from two previous publications: Dexel et al. 1985 and Dexel et al. 1989
Koshy 2005	Controlled cohort study, non-blinded	30	sc versus iv	Morphine	VAS pain intensity (0-10)	Mean difference VAS pain after 24 hours no difference between groups (sc 7.1±1.4, iv 7.6±1.3)	Sedation score (no details provided)	Sedation score no difference between groups, both groups significant improvement, no data provided. Vomiting, nausea and pruritus absent	Continuous infusion either sc or iv was effective and safe, without use of pump systems, only with bedside drip (cost-effective)	
Moulin 1991	Crossover randomized controlled	15	sc versus iv	Hydromor-phone	VAS pain intensity, pain relief (0-100)	Mean VAS pain intensity reduced from approximately 31 to 20 in both groups, pain relief approximately 72 in both groups at the end of infusion	VAS sedation, mood (0-100)	Mean VAS sedation approximately 37 (sc) and 50 (iv, not significant), mood approximately 72 (sc) and 58 (iv, not significant)	53 patients with indication for sc application, 20 included, data available for 15 patients. Infusion for 48 hours, washout with morphine, then 48 hours with other drug, double dummy technique. Infusion rates 1-35 mg/h, pain intensity, pain relief, mood and sedation significantly improved with no difference between sc and iv. Because of simplicity, technical advantages and cost-effectiveness of sc infusion iv should be abandoned	No significant difference in plasma concentrations
Bruera 1995	Crossover, randomized trial, non-blinded	23	Rectal versus sc	Morphine	VAS pain intensity (0-100), VRS (6-step, from McGill) pain intensity	Mean VAS pain intensity no difference (rectal 13.2, subcutaneously 13.3), mean VRS minimal difference (rectal 0.7, subcutaneously 0.9, p=0.0459)	VAS nausea, sedation (0-100)	VAS sedation no difference (rectal 23.2, subcutaneously 24.5), VAS nausea no difference (rectal 7.8, subcutaneously 9.0)	Mean dosage 326±69 mg (rectal) and 138±28 mg (subcutaneous), 12-hour intervals appropriate with rectal application of slow-release morphine, rectal application is a reliable, noninvasive alternative for subcutaneous application	Mean conversion ration rectal: subcutaneous was 2.4:1; power analysis included: 24 patients 80% power

Bruera 1995	Controlled cohort study, non-randomized, open	37	All patients pretreatment with sc, change to oral (21 patients) versus rectal (16)	Hydromorphone (pretreatment), change to methadone	VAS pain intensity (0-100)	VAS pain intensity reduced from 50±21 (pretreatment with hydromorphone) to 29±13 (rectal methadone) and from 51±23 (pretreatment with hydromorphone) to 39±25 (oral methadone). Total cost 86±128 Canadian funds (rectal) versus 228±253 (oral), much higher with sc hydromorphone pretreatment	Not reported	Mild sedation and constipation in all patients, other side effects not reported separately for rectal route	Mean time for change over from pretreatment with sc 3.2±3.7 days for rectal route, 6.5±3.6 days for oral. Slow switch to methadone either rectally or orally was safe, effective and a low cost alternative	Conversion factor 1.2±1.3 for sc hydromorphone /oral methadone and 3±2 for sc hydromorphone to rectal methadone
Nelson 1997	Crossover, non-randomized trial	40 iv	switched to sc	Morphine	VAS pain intensity, VRS pain intensity (none, mild, moderate, severe)	VAS 22.9±21.6 (iv) to 17.6±15.5 (sc)	VRS side effects (none, mild, moderate, severe)	Local toxicity 2 patients (sc), no significant difference in side effects. Constipation (iv 25 patients, sc 24), dry mouth (iv 23, sc anxiety/depression (iv 6, sc 6), blurred vision (iv 4, sc 1), euphoria (iv 3, sc 2), myoclonus (iv 3, sc 2), nausea/ vomiting (iv 3, sc 4), rash/pruritus (iv 3, sc 0), respiratory depression (iv 3, sc 1), urinary retention (iv 1, sc 1) 21), sedation (iv10, sc 7),	Dosage 5.05±4.75 mg/h (iv) to 5.7±5.8 (sc), 8/40 patients did not achieve stable dosage, all in all sc not different to iv	
Campbell 1983	Case reports	1	iv switch to sc	Morphine	Not reported	Equally successful pain control with sc and iv	Not reported	Mild constipation, local erythema at injection site with sc route	switched from iv to sc route, 2 months followup	
Walsh 2006	Case series, prospective	50	iv to oral (17 patients), iv to sc (16 patients), iv only (9 patients), sc only (3 patients), miscella neous (5 patients)	Morphine	Pain control (good/poor)	Pain control iv to oral: 82/18% (good/poor), iv to sc 75/13%, iv only 67/2%, sc 33/67%, misc 100/0%	Not reported	Not reported	iv to oral had mores stable pain control assessed with a variety of measures	

(continued)

Table 3. Continued

First author, year	Study design	Patients			Results: efficacy		Results: side effects			
		Patient numbers	Route	Drugs	Outcomea measures	Summary of results	Outcome measures	Summary of results	Narrative summary of results	Notes
Watanabe 1998	Case series	22	Oral, transdermal switch to sc	Fentanyl	VAS pain intensity	3/5 patients switched from transdermal to sc fentanyl good pain relief (VAS 53±15 to 10±10), the other 2 switched to other opioids. 10/17 patients switched from other opioids to sc fentanyl good pain relief (VAS 41±24 to 33±16)	Not reported	Not reported for transdermal to sc fentanyl, for other patients improvement of toxicity in 7/10 patients	3/5 patients switched from transdermal to sc fentanyl good pain relief (VAS 53±15 to 10±10), the other 2 switched to other opioids. 10/17 patients switched from other opioids to sc fentanyl good pain relief (VAS 41±24 to 33±16)	6 patients stabilized on sc fentanyl switched to transdermal fentanyl, 4 with good effect
Enting 2002	Case series	100	Oral (44), transdermal (56) switched to sc	Morphine, fentanyl, sufentanyl, hydromorphone	NRS 11-step, clinically important improvement (≤2 difference on NRS, moderate pain or less)	Pain intensity at rest decreased from 6.3 to 4.4 after 48 hours and further to 3.4 at the end of treatment, important improvement of pain at rest for 52% of patients after 48 hours and for 71% at end of treatment, important improvement of pain during movement for 43% after 48 hours and 61% at end of treatment	VRS 4-step for nausea or emesis, constipation, confusion, hallucinations, somnolence	Resolution or improvement of side effects: nausea/emesis 20/33 patients, constipation 34/50, somnolence 27/45, confusion 13/15, hallucinations 7/10, any side effect 25/78	Good improvement in efficacy and reduction of side effect following switch to parenteral opioids	Not clear how many patients received sc or iv application
Ellershaw 2002	Controlled cohort study, retrospective evaluation	94	Transde rmal (47 patients), sc (47)	Fentanyl (47 patients), diamorphine (47)	Pain (controlled/un controlled)	Frequency of controlled pain observations during last 48 hours significantly higher for transdermal fentanyl for 2/12 observation periods, no difference for the other 10 periods	Not reported	Not reported	Retrospective evaluation, matched pair building for the two groups, median dosage fentanyl 50 mg, diamorphine 30 mg. Overall little difference between groups, good pain control in both groups	

sc, subcutaneous; iv, intravenous; im, intramuscular; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale; NRS, Numerical Rating Scale.

Table 4. Studies comparing intravenous with other application routes

First author, year	Study design	Patients			Results: efficacy		Results: side effects			
		Patient numbers	Route	Drugs	Outcome measures	Summary of results	Outcome measures	Summary of results	Narrative summary of results	Notes
Elsner 2005	See Table 3	39		Morphine						
Drexel 1991	See Table 3	15		Morphine						
Koshy 2005	See Table 3	30		Morphine						
Moulin 1991	See Table 3	15		Hydromorphone						
Nelson 1997	See Table 3	40		Morphine						
Campbell 1983	See Table 3	1		Morphine						
Walsh 2006	See Table 3	50		Morphine						
Leow 1995	Case series	12	iv versus rectally	Oxycodone	Pain intensity VAS	VAS pre 5.7±2.0 / 4.7±2.2 (iv/rectal); 30 min 0.4±0.6 / 2.4±1.8; 60 min 0.4±1.2 / 0.7±0.8; 120 min 1.3±1.8 / 0.5±0.5; 240 min 2.0±2.3 / 0.4±0.4	VRS 4-step for drowsiness, lightheadedness, nausea, vomiting, pruritus, sweating	Drowsiness and lightheadedness most frequent, nausea more often with rectal administration	Both routes provided satisfactory analgesia, much more rapid onset with iv (5-8 min for 25% pain reduction) versus rectal (60-120 min)	Only single dose
Kornick 2001	Case series	15	iv switch to transdermal	Fentanyl	Pain intensity at rest / with movement 11-step NRS, satisfaction with current level of pain relief (yes/no)	Median pain at rest reduced after 24 hours from NRS 3 to 2, median pain with movement from 4 to 3	Sedation 4-step VRS, other adverse effects severity on 4-step VRS	Median sedation reduced from VRS 1 to 0 after 24 hours	Stable conversion possible	Not enough information to calculate conversion factor
Kornick 2003	Case series	9	Transdermal switch to iv	Fentanyl	Pain intensity at rest / with movement 11-step NRS	Pain ≥8 before switch (inclusion criterion) reduced to ≤4 (at rest) within 5 days in all 9 patients. 3 patients switched back because of inadequate pain relief with movement	Sedation 4-step VRS, other adverse effects severity on 4-step VRS	Sedation increased in one patient	Dosage was higher after switching to iv application, but with superior pain relief. Median time to achieve mild levels of pain at rest was 1.5 days, six patients achieved mild levels of pain with movement within 3 days.	Not enough information to calculate conversion factor
Zech 1992	Sequential cohort study	20	iv to transdermal	Fentanyl	VAS pain intensity, VRS pain relief (5-step)	VAS pain intensity decreased from 68 to 34 on day 1 (with iv PCA) and further to	VAS symptom intensity (0=never/not at all, 100=	no significant differences in side effects with VAS constipation 31±35	Intravenous titration with fentanyl provided rapid	Conversion ratio iv: transdermal 1:1 used

(continued)

Table 4. Continued

First author, year	Study design	Patients: Patient numbers	Route	Drugs	Results: efficacy: Outcome measures	Summary of results	Results: side effects: Outcome measures	Summary of results	Narrative summary of results	Notes
						26 (transdermal), then increased again to 31 on day 7.	extremely/all the time)	(day 0) to 22±34 (day1) to 13±27 (day 7), VAS nausea 4±10, 6±23, 2±9, VAS fatigue 38±36, 28±36, 26±35, VAS sweating 22±33, 25±27, 14±16	relief, conversion from intravenous to transdermal was safe and effective	
Grond 1997	Sequential cohort study	50	iv, transdermal	Fentanyl	VAS pain intensity (0=no pain, 00= pain as bad as can be)	VAS pain intensity reduced from approximately 44 (pretreatment, CI 38–50) to 32 (day 1 with iv, CI 27–37) to 22 (day 2 with transdermal, CI 17–27), 17 on day 7 and finally 13 during long-term treatment (day 85-535)	Percentage of days with symptom	No severe side effects, 9 patients local side effects (rashes or pruritus). Percentage of treatment days for constipation reduced from 40 (pretreatment) to 18 (titration period) to 10 (long-term), dry mouth 42 to 53 5o 34, nausea from 34 to 17 to 17, dyspnoea from 14 to 15 to 17, somnolence from 64 to 48 to 58, sweating from 30 to 26 to 28, vertigo from 18 to 12 to 5, vomiting from 18 to 11 to 5, diarrhoea from 6 to 5 to 4, pruritus from 2 to 7 to 2. Respiratory rates < 8 in 3 patients. Dropouts because of surgical intervention (7 patients), poor compliance (6), inadequate pain relief (4), respiratory depression (1), pain relief with radiotherapy (1), referral to other hospital (1)	Treatment duration 3-535 days, dosage increased from 3.1+2.2 mg/d in first week to 7.8+2.6 in 45th week. Iv titration was useful for dose finding, and transdermal application safe and effective	Conversion ratio fo 1:1.5 used from iv to transdermal, but 3 patients with respiratory rate<8/minute, so 1:1 is safer for conversion

iv, intravenous; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale; NRS, Numerical Rating Scale.

subcutaneous application, including two studies with a randomized controlled methodology.[25,28] As described in the section on subcutaneous application, no differences were reported between these two routes.

Only one study compared intravenous and rectal opioid application,[39] finding no difference in pain relief, but faster onset of analgesia with the intravenous route. Pain relief of 25% was achieved in 5–8 minutes with intravenous application compared with 60–120 minutes with rectal application. However, this study included only 12 patients and a single dose application of oxycodone.

A comparison of intravenous and transdermal route for opioid application was possible for four studies, predominantly because intravenous titration was used for dose finding before the initiation of transdermal therapy. Only one study reported conversion from transdermal to intravenous application.[40] The nine patients in this study were suffering from severe pain in spite of transdermal treatment. Following the switch to intravenous application higher dosages of fentanyl were required, resulting in superior pain relief with only mild pain at rest after 1.5 days and good pain relief with movement in six of the nine patients.

The other three studies used intravenous application of fentanyl before patients were switched to transdermal application.[41–43] All three studies reported good pain relief compared with pretreatment and stable analgesia after switching to transdermal application. Side effects were reduced with intravenous application compared with pretreatment regimens. Lower sedation scores were reported in all three studies, less constipation in two[41,43] and less dry mouth and vertigo in one.[41] Less nausea was reported in one study[41] and slightly higher intensity of nausea in another.[43]

A conversion ratio for oral:intravenous morphine between 2 : 1 and 3 : 1 is backed up by some papers, who reported a conversion of 2.9.[44] For fentanyl the study of Zech et al.[43] has used a 1 : 1 conversion ratio from intravenous to transdermal with comparable efficacy and tolerability. The subsequent study of Grond et al.[41] used a higher conversion ratio of 1 : 1.5, but found some complications with respiratory depression with this ratio, and concluded that the 1 : 1 ratio would be preferable.

The literature search identified another nine studies with a total of 549 patients reporting on the use of the intravenous application route with morphine, hydromorphone and in some cases also methadone or oxycodone. The survey from Meuret and Jocham[45] reported on 143 patients treated with either subcutaneous or intravenous application for treatment durations of up to 437 days, using patients controlled analgesia with morphine with good effect. Only 4% of patients reported insufficient pain relief. However, results from both application routes are not reported separately, and so comparison of adverse effects was not possible. Constipation, fatigue and nausea were predominant for the whole set of patients. Ferris et al.[46] published a retrospective evaluation of 135 patients treated either with subcutaneous or intravenous application of morphine or hydromorphone for more than 6 days, with 35 patients receiving opioids via both routes. Again data were not reported separately for the application routes, good efficacy was seen with both routes and the profile of adverse events was similar to other opioid surveys.

Rectal route

The Cochrane review from Wiffen and McQuay[15] included two studies comparing oral with rectal application of morphine.[47,48] However, one study was published in Japanese.[47] The other study with 34 patients reported that pain relief was achieved significantly faster and was maintained better in the rectal group.[47]

The literature search in this study identified four studies with 174 patients that compared alternative application routes, using morphine, oxycodone or methadone (Table 5). The studies of Bruera et al.[31] and of Leow et al.[39] reporting similar efficacy and tolerability with subcutaneous or intravenous application have been described in detail above. The workgroup of Bruera[32] also switched patients pretreated with subcutaneous hydromorphone to either oral or rectal methadone and found that both routes were safe and effective, but that the mean time for change was much shorter for rectal compared with oral application. Pannuti et al.[49] also found similar efficacy with oral, rectal and sublingual application of morphine in a controlled study with 102 patients who received treatment for at least 10 days. Drowsiness and dry mouth were reported more often with the rectal application, and two patients discontinued rectal application due to local intolerance. However, the patient group with rectal application reported the highest reduction of pain intensity.

Only one study reported a conversion ratio with 2.4:1 as the ratio of rectal : subcutaneous morphine.[31] The literature search also found another two studies with 56 patients reporting on the rectal application of morphine or methadone, but without a comparison of alternative routes.

Transdermal route

In the Cochrane review on oral morphine for cancer pain[15] three studies with a total of 333 patients were reported comparing oral morphine with transdermal fentanyl.[50–52] However, differences such as less

Table 5. Studies comparing rectal with other application routes

First author, year	Study design	Patients			Results: efficacy		Results: side effects			
		Patient numbers	Route	Drugs	Outcome measures	Summary of results	Outcome measures	Summary of results	Narrative summary of results	Notes
Wiffen 2007	Systemic review	5 studies (413 patients)	Oral versus transdermal (3 studies, 333 patients), oral versus rectal (2 studies, 80 patients)	Morphine, fentanyl	Miscellaneous	Rectal faster onset and longer duration of pain relief, transdermal similar efficacy compared to oral	Miscellaneous	Transdermal with less constipation		
Bruera 1995	Crossover, randomized trial, non-blinded	23	Rectal versussc	Morphine	VAS pain intensity (0-100), VRS (6-step, from McGill) pain intensity	Mean VAS pain intensity no difference (rectal 13.2, subcutaneously 13.3), mean VRS minimal difference (rectal 0.7, subcutaneously 0.9, $p = 0.0459$)	VAS nausea, sedation (0-100)	VAS sedation no difference (rectal 23.2, subcutaneously 24.5), VAS nausea no difference (rectal 7.8, subcutaneously 9.0)	Mean dosage 326±69 mg (rectal) and 138±28 mg (subcutaneous), 12-hour intervals appropriate with rectal application of slow-release morphine, rectal application is a reliable, noninvasive alternative for subcutaneous application	Mean conversion ration rectal: subcutaneous was 2.4:1; power analysis included: 24 patients 80% power
Leow 1995	Case series	12	iv versus rectally	Oxycodone	Pain intensity VAS	VAS pre 5.7±2.0 / 4.7±2.2(iv/rectal); 30 min 0.4±0.6 / 2.4±1.8; 60 min 0.4±1.2 / 0.7±0.8; 120 min 1.3±1.8 / 0.5±0.5; 240 min 2.0±2.3 / 0.4±0.4	VRS 4-step for drowsiness, lightheadedness, nausea, vomiting, pruritus, sweating	Drowsiness and lightheadedness most frequent, nausea more often with rectal administration	Both routes provided satisfactory analgesia, much more rapid onset with iv (5-8 min for 25% pain reduction) versus rectal (60-120min)	Only single dose

Bruera 1995	Controlled cohort study, non-randomized, open	37	All patients pretreatment with sc, change to oral (21 patients) versus rectal (16)	Hydromorphone (pretreatment), change to methadone	VAS pain intensity (0-100)	VAS pain intensity reduced from 50±21 (pretreatment with hydromorphone) to 29±13 (rectal methadone) and from 51±23 (pretreatment with hydromorphone) to 39±25 (oral methadone). Total cost 86±128 Canadian funds (rectal) versus 228±253 (oral), much higher with sc hydromorphone pretreatment	Not reported	Mild sedation and constipation in all patients, other side effects not reported separately for rectal route	Mean time for change over from pretreatment with sc 3.2±3.7 days for rectal route, 6.5±3.6 days for oral. Slow switch to methadone either rectally or orally was safe, effective and a low cost alternative	Conversion factor 1.2±1.3 for sc hydromorphone/ oral methadone and 3±2 for sc hydromorphone to rectal methadone
Pannuti 1982	Controlled cohort study	102	Oral (37), rectal (37), sublingual (28)	Morphine	Pain intensity, 5-step VRS for physician rating, VAS for patient rating	Oral route (11 weeks follow-up): pain intensity from VAS 7.8 to 3.2 ($p<0.01$); rectal route (8 weeks follow-up): pain intensity from VAS 9.3 to 1.3 ($p<0.001$); sublingual route (5 weeks follow-up): pain intensity from VAS 7.8 to 2.7 ($p<0.001$)	Percentage of patients	Constipation (oral/rectal/sublingual) 81/89/71% of patients, drowsiness 59/73/71%, dry mouth 46/86/61%, vomiting 30/24/18%; dropout: oral route 2 patients because of psychosis, 3 vomiting, rectal route 2 patients local intolerance	All routes were effective, authors state more rapid and significant pain remission for the sublingual route, although rectal was superior in physicians' assessment	

sc, subcutaneous; iv, intravenous; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale; NRS, Numerical Rating Scale.

constipation and less sedation with transdermal fentanyl in one study and problems with managing the change to fentanyl in another were attributed by the authors more to the change of opioid than to the change of route.

In the literature search seven studies with 310 patients were found comparing transdermal with other alternative application routes (Table 6). Four of these studies compared transdermal with intravenous application and have been described in detail in the section on intravenous application.[40–43] Two others compared the transdermal with the subcutaneous route and details are provided in the section on subcutaneous application.[17,35] In a retrospective chart evaluation, Ellershaw et al.[36] matched pairs of patients switched from oral morphine to transdermal fentanyl with those switched to subcutaneous application of diamorphine and found little difference between the two groups.

The literature search identified another 13 studies with a total of 801 patients treated with transdermal opioid application. Among these were three larger surveys using transdermal buprenorphine, which was part of the portfolio for the registration of the new transdermal therapeutic system.[53–55] These studies demonstrated a significant higher number of responders compared with placebo in a large number of patients, with a profile of adverse events that is similar to opioid application via other routes. Local symptoms at the application site were reported in several studies, with an incidence for erythema ranging from 3% (Likar et al.[53]) to 27.3% of patients (Sittl et al.[55]). One study with the buprenorphine patch reported fewer local side effects with cancer patients compared with non-cancer patients.[56] Pruritus at the patch site was reported with a similar incidence ranging from 3.7% to 24.8% of patients. Other local side effects such as swelling or exanthema were reported only rarely.

In a recent study with cachectic patients[57] the mean dosage was significantly higher in cachectic patients ($96 \pm 29\,\mu g/h$) compared with normal weight ($42 \pm 10\,\mu g/h$), whereas plasma concentration were significantly lower in the cachectic patients. The authors concluded that absorption from the transdermal system is impaired in cachectic patients.

Transmucosal or sublingual route

Opioid application via the oral, sublingual or nasal mucosa was compared with other routes in only one study. Pannuti et al.[49] compared oral, rectal and sublingual morphine in a controlled study in 102 patients, and found a more rapid and more significant pain remission with the sublingual application compared with rectal or oral routes in the regression analysis of pain behaviour.

The literature search identified another two studies using the transmucosal fentanyl application in 39 patients[58] or the sublingual application of fentanyl in 10 patients,[59] but both did not compare this with alternative routes.

Discussion

The literature search found a large number of studies, although only a few of those publications offered a comparison of different alternative routes for opioid treatment. Even though morphine was predominant in these studies, a large number of opioids such as hydromorphone, oxycodone, methadone, fentanyl, buprenorphine, diamorphine, sufentanil or ketobemidone were used. Intermittent injections, infusions with or without syringe pump devices were used for parenteral application routes, and different solutions, tablets or capsules with different pharmacokinetic properties were used for sublingual or rectal application.

No study used intramuscular injections in clinical practice. In only one case was intramuscular morphine administered and the in description of the pharmacokinetics properties of this route, it was reported as less effective as expected.[49]

The best evidence base was available for the subcutaneous route with a systematic review and three randomized controlled trials. A comparison of subcutaneous and intravenous routes found no differences, confirming that both routes are feasible, effective and safe. As the risk of complications is lower with subcutaneous application, this route should be preferred. For patients with a port system or an indwelling venous line for other therapeutic indications the intravenous administration route would be an alternative.

Opioid administration with the rectal route was investigated in four studies, one of which was a randomized controlled, crossover study. The publications described comparable efficacy and safety with the parenteral and rectal routes. Onset of analgesia was described as much faster following a single dose application of oxycodone intravenously in one study. On the other hand, rectal application seems to have a faster onset than the oral application[47] and the mean time to change over from subcutaneous to rectal administration took only half as long as the change over from subcutaneous to oral administration.

In spite of the wealth of research on transdermal opioid application, only seven studies comparing transdermal with other alternative routes were included in this review. For the transdermal route it seems difficult to differentiate between effects of the opioid switch and those of the route change. However, some studies

Table 6. Studies comparing transdermal with other application routes

		Patients			Results: efficacy		Results: side effects			
First author, year	**Study design**	**Patient numbers**	**Route**	**Drugs**	**Outcome measures**	**Summary of results**	**Outcome measures**	**Summary of results**	**Narrative summary of results**	**Notes**
Wiffen 2007	Systemic review	5 studies (413 patients)	Oral versus transdermal (3 studies, 333 patients), oral versus rectal (2 studies, 80 patients)	Morphine, fentanyl	Miscellaneous	Rectal faster onset and longer duration of pain relief, transdermal similar efficacy compared to oral	Miscellaneous	Transdermal with less constipation		
Kornick 2001	See Table 4	15		Fentanyl						
Kornick 2003	See Table 4	9		Fentanyl						
Zech 1992	See Table 4	20		Fentanyl						
Grond 1997	See Table 4	50		Fentanyl						
Watanabe 1998	See Table 3	22		Fentanyl						
Enting 2002	See Table 3	100		Morphine, fentanyl, sufentanyl, hydromorphone						
Ellershaw 2002	Controlled cohort study, retrospective evaluation	94	Transdermal (47 patients), sc (47)	Fentanyl (47 patients), diamorphine (47)	Pain (controlled/ uncontrolled)	Frequency of controlled pain observations during last 48 hours significantly higher for transdermal fentanyl for 2/12 observation periods, no difference for the other 10 periods	Not reported	Not reported	Retrospective evaluation, matched pair building for the two groups, median dosage fentanyl 50 mg, diamorphine 30 mg. Overall little difference between groups, good pain control in both groups	

sc, subcutaneous.

compared transdermal opioid therapy with subcutaneous or intravenous administration of the same drug. This allows for a clear understanding that efficacy and tolerability are similar for both routes. More information on this will be provided in a separate systematic review on transdermal treatment.

Transmucosal or sublingual application was investigated only rarely in comparison with other application routes. Similarly, no reports at all were found for intranasal opioid application with the proposed search strategy. This is astonishing, as in recent years much research on these application routes has been performed for the treatment of breakthrough pain with the high number of new therapeutic systems that have been introduced in the last 2 years. However, these new systems are indicated for breakthrough pain treatment, but not for treatment of continuous pain, and thus may not be suitable alternative routes for patients not able to use the oral route but requiring continuous around the clock analgesia. Still, this lack of publications points to a gap in the research agenda which has to be addressed.

The new therapeutic systems have been compared directly against other alternative forms in a few studies on breakthrough pain, for example comparing intransasal fentenyl spray with transmucosal or intravenous application[60,61] or reporting long-term efficacy.[62] However, breakthrough pain will be considered in a separate systematic review and so studies on breakthrough pain have not been considered in our review.

The side effect profile seemed to be very similar for the subcutaneous, intravenous, rectal or transdermal routes, with sedation, nausea, vomiting, dry mouth being most frequent as typical opioid-related side effects. Local side effects were reported for rectal application as well as for subcutaneous and transdermal administration, with erythema and pruritus being most frequent.

Following the clinical experience of the experts, most routes seem to have clear indications, taking into account their specific pharmacokinetic properties. For example, transdermal administration provides stable analgesia, but reacts only sluggishly to dose changes, and this makes it suitable predominantly for patients with chronic stable pain. Transmucosal fentanyl provides a faster onset of analgesia, but is more fluctuant than other administration forms.

This review included not only randomized controlled trials but also non-randomized trials, and the low methodological quality of many of the studies included may have introduced bias. We did not assess potential bias across the studies. The setting and the time frame for the studies varied widely, and studies used a wide range of different outcome parameters on effectiveness as well as on safety, thus preventing meaningful meta-analysis. Randomized controlled trials with adequate size and methodology comparing major alternative routes in a head-to-head comparison are lacking.

Studies were retrieved only from Medline (PubMed) and only in English, and other publication databases might have added to the literature retrieved. Similarly, we did not contact authors or search handbooks. However, the consistency of the results clearly supports the conclusions from the review at least for subcutaneous, intravenous, transdermal and rectal administration routes.

Conclusion

In conclusion, the systematic review found good evidence that subcutaneous administration of morphine or other opioids will be an effective alternative for cancer patients if oral treatment is not possible.

However, for a number of patients intravenous, rectal or transdermal therapy will offer a good alternative to the subcutaneous route. The review found no significant differences in efficacy or side effects between the alternative application routes.

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