Clinical Guideline

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

Appendix E – Evidence tables
May 2012

Developed for NICE by the National Collaborating Centre for Cancer

Contents

3.1 Communication 4

1: What information do patients with advanced and progressive disease who require strong opioids, or their carers, need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid? 4

3.3 Starting strong opioids – titrating the dose with immediate-release, sustained-release or transdermal patches 7

2a: Are immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or opioid patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids? 7

3.4 First-line maintenance treatment 38

2b: Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids? 38

3.5 First-line treatment if oral opioids are not suitable – transdermal patches 50

2c: Are fentanyl patches more effective than 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? 50

3.6 First-line treatment if oral opioids are not suitable – subcutaneous delivery . 53

2d: Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable? 53

3.7 First-line treatment if oral opioids are not suitable – transdermal patch versus subcutaneous delivery 54

2e: Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable? 54

3.8 First-line treatment for breakthrough pain in patients who can take oral opioids 55

2f: What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)? 55

3.9 Management of constipation 60

3a: 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? 60

3.10 Management of nausea 61

3b: 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? 61

3.11 Management of drowsiness 62

3c: Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect? 62

3.1 Communication

Review question 1: What information do patients with advanced and progressive disease who require strong opioids, or their carers, need to: 1) Consent to opioid treatment and 2) monitor the effectiveness and side effects of the opioid?

Evidence table 1

Citation: Bender, J. L., Hohenadel, J., Wong, J., Katz, J., Ferris, L. E., Shobbrook, C., Warr, D., and Jadad, A. R. What Patients with Cancer Want to Know About Pain: A Qualitative Study. Journal of Pain and Symptom Management 35[2], 177-187. 2008.
Design: Qualitative study **Country**: Canada **Aim**: To explore what patients with breast cancer want to know about pain.
Inclusion criteria Patients with pain (of any kind and severity) associated with breast cancer or its treatment, ≥ 18 years old, and who were able to understand spoken and written English. Recruitment was stopped when data saturation was reached.
Exclusion criteria None listed
Population An opportunity sample of N = 18 patients with breast cancer recruited from the breast cancer and pain clinics from June to October 2003: N = 14 were > 55 years old; years since diagnosis: 0-5 (N = 8), 6-10 (N = 5), 11+ (N = 5); N = 10 had metastatic breast cancer; treatments received: Surgery (N = 17), radiation therapy (N = 12), chemotherapy (N = 14); N = 9 had > 1 pain; pain intensity at its worst (measured on 4-point verbal scale [none, mild moderate, severe]): Mild (N = 2), severe (N = 16); pain intensity in the last 7 days: Mild (N = 10), moderate (N = 6), severe (N = 2); pain intensity at the interview: None (N = 1), mild (N = 13), moderate (N = 2), severe (N = 2); current analgesic therapy: None (N = 2), NSAIDs or acetaminophen (N = 3), opioid (N = 13); attributed cause of pain: Cancer (N = 8), treatment (N = 7), unknown (N = 2), unrelated (N = 1).
Interventions 60-minute (approximately), audio-recorded semi-structured interviews were conducted by one person either following a scheduled clinic appointment or by telephone. Open-ended questions were used to guide the interview. Participants were asked about their experiences with pain, related questions and concerns, specific information they wished they knew more about or had known earlier, questions they asked their health professionals, and any unanswered questions. Clarification probes and follow-up questions were used to clarify and explore issues in greater depth and to verify our understanding of the information being collected. *Only the result relevant to the clinical question will be reported.*
Outcomes See **Results** section**.**
Results - The patients expressed a desire to know all options for pain control available, how the drugs or treatments work, expected side effects, and under what circumstances they are used to treat pain. Many described a period of time when they endured severe pain because they were not aware of the treatment options available. - Several practical questions about the use and administration of analgesic medication were raised, 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. - ‘‘‘How long before it starts working?’ ‘How long it’s going to work for?’. ‘If I’m taking my pill at 8:00 in the morning, ‘when should I feel relief?’ ‘An hour later, twenty minutes later?’ And if I’m taking them every twelve hours, ‘Is it going to last the twelve hours?’’’[Participant 18]
General comments This qualitative study appears to have been conducted to a high quality using solid qualitative study methodology, including pilot testing of the interview guide to ensure the clarity of the questions and follow-up probes, on-going development and integration of new questions in successive interviews as new issues and themes emerged, and independent coding of the majority of the transcripts by more than one researcher. However, the population and main aims of the study do not exactly match those of the clinical question, although the majority of the patients were receiving opioid

treatment, therefore the data provided by this study is very limited in this context.

References of Included Studies (For systematic reviews): N/A

Citation: Blanchard, H. and Batten, B. Designing and producing a patient leaflet on morphine. European Journal of Palliative Care 3[3], 106-108. 1996.

Design: Qualitative study
Country: United Kingdom
Aim: To investigate cancer patients' knowledge of morphine.

Inclusion criteria
Patients with terminal cancer.

Exclusion criteria
Patients who were confused, too ill to participate (mentally or physically) or who declined.

Population
N = 47 patients, 31/47 patients were taking or had previously taken morphine and 16/47 patients were not taking morphine.

Interventions
15-minute interviews were conducted by one person over a 3-week period. Patients were individually interviewed at several UK locations and settings (inpatients, day-care unit, oncology outpatients, hospice and at home).
The interviews were carried out according to the following format:

1) An open question, giving the patient an opportunity to ask questions or express concerns about morphine
2) Structured questions on knowledge about morphine. *The result of these are not relevant to the clinical question so will not be reported.*

Outcomes See **Results** section**.**

Results
17/31 patients taking or having previously taken morphine provided responses to the open question.
The most common concerns or questions were:
- Will I become addicted? (8)
- What are the side-effects? (8, including more specific questions, for example about constipation)
- Am I near the end? (4)
- Can I drink alcohol? (2)

7/16 patients not on morphine volunteered the following potential questions/concerns:
- Am I 'near the end'?
- Is it a poison?
- What are the side-effects?

General comments
This short paper provides so little detail about the methods employed and the results that it is not possible to properly appraise the study comprehensively.

References of Included Studies (For systematic reviews): N/A

Citation: Reid, C. M., Gooberman-Hill, R., and Hanks, G. W. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. Annals of Oncology 19[1], 44-48. 2008.

Design: Qualitative
Country: United Kingdom
Aim: To explore the factors influencing the decision to accept/reject morphine when first offered to patients with cancer.

Inclusion criteria
Participants were recruited from a pain management trial that took place in a UK oncology centre. Patients who had uncontrolled pain caused by cancer and were only taking paracetamol or a nonsteroidal anti-inflammatory drug for pain were eligible for the trial. On entering, they were randomized to either the traditional World Health Organization three-step analgesic ladder and prescribed a step II analgesic (cocodamol) or to an experimental two-step approach and prescribed a step III opioid (oxycodone). Participants were informed that if they agreed to take part, they had a 50/50

chance of being allocated to oxycodone, described in the patient information sheet as being similar to 'morphine'. All patients who both entered and declined participation in the trial were approached to request an interview.

Exclusion criteria None listed

Population
- N = 29 were approached about the interview study and 18 took part. Of these 18, 12 had also agreed to participate in the two-step trial. 5 patients who entered the two-step trial did not participate because they died soon after study entry. 6 other patients were approached about the interviews but did not take part (N = 2 died very quickly, N = 4 did not want to take part).
- N = 18 patients: Age range: 55- 82 years, all white, 9 women. All participants described how pain had a significant impact on their lives, often resulting in loss of mobility, function or role. N = 10 had recently had news of disease spread. Analgesics at time of interview: Oxycodone (N = 5), regular cocodamol plus 'as required' morphine (N = 2), regular modified-release morphine (N = 2), regular normal-release morphine (N = 1), paracetamol (N = 1), paracetamol plus 'as required' morphine (N = 2), cocodamol (N = 2), ibuprofen 'as required' (N = 1), morphine 'as required' (N = 1), nil (n = 1).

Interventions
The majority of the participants were interviewed in their own homes by one of the authors and most took place within 2 weeks of their trial recruitment interview. The interviews were conducted with the aid of a topic guide and participants were asked to describe their pain and its impact upon their lives, their recollections of the consultation when the trial was discussed, their associations with morphine, the flexibility of their decision to commence or delay opioids and the influence of others upon that decision. Interviews were audio-recorded, transcribed verbatim and anonymised. *Only the result relevant to the clinical question will be reported.*

Outcomes See **Results** section**.**

Results
- The professional was mentioned often during the interviews. Participants described the way in which professionals had communicated about pain, how opioids were offered (in particular whether or not they were offered as choice), and discussed trust in their professional.
- Participants preferred unhurried consultations in which pain was seen as important. Some did not expect their pain to be addressed during oncology clinics because they perceived the staff to already have high workloads.
- 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 commenced at a 'low dose' and opioids could be discontinued if side-effects developed.
- Participants 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?" Harvey
- Half of the participants mentioned trust in the professional as an important factor in their decision to take opioids. For some, trusting the professional allowed them to make their own decision to commence, whereas for others, trust meant that they could allow that the professional to make the decision on their behalf: "No, no I'd think to myself, ''Well they're putting me onto something else which is a stronger drug to help me.''.. And I just accepted that. I mean when I go to any doctor—well most doctors anyway—.. I always go in there with the idea that they know what they're doing." Jim

General comments
This qualitative study appears to have been conducted to a high quality using solid qualitative study methodology, including ensuring data saturation, independent data coding by more than one researcher, and negative case analysis However, the main aims of the study do not exactly match those of the clinical question therefore the data provided by this study is very limited in this context.

References of Included Studies (For systematic reviews): N/A

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

Review question 2: What is the most effective first-line opioid treatment in patients with advanced and progressive disease who require strong opioids?

2a: Are immediate-release opioids (morphine/oxycodone) more effective than sustained-release opioids (morphine/oxycodone) or opioid patches (fentanyl/buprenorphine) as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids?

Evidence table 2

Citation: Arkinstall, W. W., Goughnour, B. R., White, J. A., Stewart, J. H., Arkinstall, W. W., Goughnour, B. R. et al. (1989). Control of severe pain with sustained-release morphine tablets v. oral morphine solution. *CMAJ Canadian Medical Association Journal, 140,* 653-657.

Design: Randomised, double-blind/double dummy cross-over study
Country: Canada
Aim: To compare the efficacy of sustained-release (SR) morphine sulphate tablets given every 12 hours to morphine sulphate solution given every 4 hours

Inclusion criteria

- Age ≥ 19 years
- Analgesic regimen ≥ 60mg/day of orally given morphine
- Written informed consent

Exclusion criteria

- Inability to tolerate orally given morphine
- History of widely fluctuating pain severity requiring parenteral administration of opiates
- Scheduled to receive chemotherapy or radiation therapy within 1 month

Population

- 29 male and female adults with chronic severe pain (underlying illnesses included cancer (76%), chronic severe back pain (6%), multiple sclerosis (6%), astrocytoma (6%), postherpetic neuralgia (6%)).

Interventions

- SR morphine administered every 12 hours (7am and 7pm)

Versus

- IR morphine administered every 4 hours (starting at 7am)

Supplemental IR morphine for breakthrough pain

Outcomes

- Pain intensity (measured at 7am, 11am, 3pm, 7pm, 11pm using a VAS (10cm long with the words "no pain" and excruciating pain" at each end), and the Present Pain Intensity (PPI) index of the McGill-Melzack Pain Questionnaire consisting of 6 adjectives (0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating)
- Supplemental doses of morphine
- Side effects (0 = none to 6 = intolerable)
- Preference

Results

Pain intensity – VAS (10cm long with the words "no pain" and excruciating pain" at each end)

	SR	IR
Pain intensity - mean (SD)	1.36 (SD = 1.68)	1.57 (SD = 1.82)

The difference was not statistically significant (P = not reported)

Supplemental morphine

	SR	IR

Supplemental morphine – doses (total mg morphine)	84 (total 2330 mg morphine)	72 (total 2320 mg morphine)

The difference was not statistically significant (P = not reported)

Side effects (0 = none to 6 = intolerable)
The authors reported that only two side effects were serious enough t o warrant statistical analysis.

Side effect	SR	IR
Nausea - mean (SD)	0.44 (SD = 1.23)	0.58 (SD = 1.32)
Tiredness - mean (SD)	0.58 (SD = 1.21)	0.64 (SD = 1.30)

Neither difference was statistically significant (P = not reported)

Preference
Preferred the SR phase of treatment - 8/14 (57%)
Preferred the IR phase of treatment - 6/14 (43%)

General comments

- Double blind
- Method of allocation and concealment were unclear
- Only 17/29 (59%) completed the study
- Reasons for withdrawals were fully reported
- ITT analyses were not performed

Citation: Christrup, L. L., Sjogren, P., Jensen, N. H., Banning, A. M., Elbaek, K., Ersboll, A. K. et al. (1999). Steady-state kinetics and dynamics of morphine in cancer patients: is sedation related to the absorption rate of morphine? *Journal of Pain & Symptom Management, 18,* 164-173.

Design: Randomised, double-blind/double dummy cross-over study
Country: Denmark
Aim: To compare the steady state pharmacokinetics of morphine and its metabolites, as well as pharmacodynamic responses (pain relief, sedation and reaction times), after administration of immediate-release (IR) and sustained-release (SR) tablets in cancer patients

Inclusion criteria

- Outpatients
- Severe cancer related pain
- Stabilised on oral morphine
- Informed consent

Exclusion criteria

- Significant renal or hepatic impairment
- Severe respiratory disease
- Received radiation therapy or chemotherapy within 4 weeks
- Disease expected to influence absorption, metabolism or elimination of morphine

Population

- 18 male and female adult outpatients with cancer related pain

Interventions

- SR morphine tablets every 12 hours

Versus

- IR morphine tablets every 6 hours

Outcomes

- Pain intensity (100mm VAS ranging from 0mm = no pain to 100mm = worst pain imaginable)
- Sedation (100mm VAS ranging from 0mm = completely awake to 100mm = impossible to stay awake)
- Side effects (recorded if spontaneously reported)
- Overall impression of the medication (very good, good, fair, bad, extremely bad)
- Pharmokinetics

- Pharmacodynamics

Results

Pain intensity

There were no significant differences between the IR and SR formulation with respect to pain intensity (data not reported)

Side effects

Reported side effects were constipation, nausea, myoclonus and fatigue. These were not reported by treatment. There were no significant differences between the IR and SR formulation with respect to side effects.

Overall impression of the medications

There was no difference in terms of patients overall impressions of the two treatments

General comments

- Double blind (using the double dummy technique)
- Methods of sequence generation and allocation concealment were unclear
- All patients entered a 7-day run-in period to confirm that their daily morphine dose requirements were stable before entry into the study
- Only data related to pharmacodynamics was reported
- Crossover to alternate tablet occurred on the morning of study day 5
- During the study, patients were not allowed to take any other medication containing morphine. Ketobemidone and acetaminophen were used for breakthrough pain

Citation: Cundiff, D., McCarthy, K., Savarese, J. J., Kaiko, R., Thomas, G., Grandy, R. et al. (1989). Evaluation of a cancer pain model for the testing of long-acting analgesics. The effect of MS Contin in a double-blind, randomized crossover design. *Cancer, 63,* 2355-2359.

Design: Randomised, double-blind/double dummy cross-over study
Country: USA
Aim: To compare oral sustained-release (SR) morphine sulphate tablets every 12 hours to IR morphine sulphate tablets every 4 hours in patients with cancer pain.

Inclusion criteria

- Age ≥ 18 years
- Required regular opioid analgesics
- Chronic cancer pain

Population

- 23 male and female adults with cancer related pain. Some used regular opioid analgesics at baseline (unclear exactly how many)

Interventions

- SR morphine tablets every 12 hour

Versus

- IR morphine tablets every 4 hours

The first day's dose was calculated by means of a standard conversion table, to be approximately one third the morphine equivalent of the previous daily narcotic dose or at least 30mg morphine every 12 hours

After achievement of acceptable analgesia and its maintenance for 48 hours in the first study arm, patients were switched to the alternate treatment regimen

Supplemental IR morphine for breakthrough pain was provided on an "as needed" basis

Outcomes

- Pain intensity (0 = none; 1 = light; 2 = moderate; 3 = severe)
- Pain frequency (0 = none; 1 = occasional; 2 = frequent; 3 = constant)
- Total morphine sulphate dose
- Rescue fraction
- Rescue dose
- Side effects

Results

Pain intensity (0 = none; 1 = light; 2 = moderate; 3 = severe)

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Mean pain intensity	2.21 ± 0.19	1.71 ± 0.16	0.79 ± 0.15	0.50 ± 0.17

The differences were not statistically significant (P = not reported)

Pain frequency (0 = none; 1 = occasional; 2 = frequent; 3 = constant)

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Mean pain frequency	2.14 ± 0.18	1.64 ± 0.17	1.00 ± 0.23	0.71 ± 0.27

The differences were not statistically significant (P = not reported)

Total morphine sulphate dose

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Total morphine sulphate dose (mg)	200 ± 51	275 ± 82	369 ± 113	496 ± 130

The difference was not statistically significant in the first 24 hours (P = not reported)
The difference in the last 24 hours was statistically significant ($P \leq 0.05$)

Rescue fraction

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Rescue fraction (%)	39	28	11	5

The differences were not statistically significant (P = not reported)

Rescue dose

	First 24 hours		Last 24 hours	
	SR	IR	SR	IR
Rescue dose (mg)	78 ± 24	77 ± 27	39 ± 14	23 ± 9

The differences were not statistically significant (P = not reported)

Side effects

Side effect	Duration (days)	No. patients	Medication phase
Dizziness	1	1	IR
Drowsiness	4	1	IR
Constipation	3.5	1	SR
Pruritus	1	1	IR

General comments

- Double blind
- Method of allocation and concealment were unclear
- Only 14/23 (61%) completed the study
- Reasons for withdrawals were fully reported
- ITT analyses were not performed

Citation: Dalton, R., Etzell, P., Loprinzi, C., Miser, A., Therneau, T., Dose, A. et al. (1989). Single-dose trial of sustained-release morphine sulphate for cancer pain relief [abstract]. *Proceedings of the American Society of Clinical Oncology, 8,* 336 **(Abstract)**

Design: RCT (parallel groups)
Country: USA

Aim: To compare the analgesic efficacy and toxicity of 30mg immediate-release (IR) morphine sulphate to 30 mg sustained-release (SR)-, 60 mg SR-, and 90 mg SR morphine.

Inclusion criteria
Not reported

Exclusion criteria
Not reported

Population
- 68 patients with cancer related pain

Interventions
This was a SINGLE DOSE RCT
- 30mg IR morphine sulphate
- 30 mg SR morphine sulphate
- 60 mg SR morphine sulphate
- 90mg SR morphine sulphate

Outcomes
- Pain relief (0-4 VAS anchored at opposite ends by "no relief" and "pain free" and a Likert scale) – rated hourly
- Side effects (0-4 VAS anchored at opposite ends by "none" and "severe"

Results

	Hours to 50% relief		Side effects
Group	**Likert Scale**	**Visual Analogue Scale**	
30mg IR (n = 48)	3.8	3.6	2.8
30mg SR (n = 45)	3.6	3.4	2.3
60mg SR (n = 47)	4.4	3.8	3.5
90mg SR (n = 47)	6.1	5.3	4.7

The data from the trial show that single doses of 90mg SR morphine gave slightly improved analgesia ($p < 0.001$) and increased toxicity ($p < 0.001$) when compared to 30mg IR morphine. The other doses of SR morphine did not significantly differ from IR morphine in toxicity or duration (all $p > 0.15$)

General comments
- Abstract only
- Single dose study
- Double blinded
- Method of randomisation and allocation concealment was unclear
- An initial un-blinded test dose of 30mg IR morphine enabled exclusion of patients with grossly inadequate pain relief or major toxicity

Citation: Deng YP, Xu GZ, Wang, K, et al. The steady-state concentration of morphine sulphate tablets and its clinical analgesic effect in cancer patients. Chinese Pharmaceutical Journal 32: 356-9. 1997.

Design: RCT (parallel groups; abstract)
Country: China
Aim: to compare immediate-release morphine sulphate (IRMS) with sustained release morphine (SRMS) cancer patients with moderate-severe pain.

Inclusion criteria
Not reported

Exclusion criteria

Not reported

Population

N = 17

Interventions

SRMS: 30 mg sustained-release oral morphine 12 hourly for 7 days.
IRMS: 10 mg immediate-release oral morphine 4 hourly for 7 days.

Outcomes

Results

"The effective analgesic rate (sum of rates of grade 2~4 pain relief) of both CRMS [= SRMS] and IRMS on the 5th day medication was 100%" (p 356).

General comments

These data are only included in abstract form as the full article is published in Chinese. It is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

References of Included Studies (For systematic reviews): NA

Citation: Deschamps, M., Band, P. R., Hislop, T. G., Rusthoven, J., Iscoe, N., Warr, D. et al. (1992). The evaluation of analgesic effects in cancer patients as exemplified by a double-blind, crossover study of immediate-release versus controlled-release morphine. *Journal of Pain & Symptom Management, 7,* 384-392.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: Canada
Aim: To compare the effects of sustained-release (SR) and immediate-release (IR) morphine preparations in adult patients with moderate to severe cancer pain and report methodological approaches to pain evaluation

Inclusion criteria

- Age ≥ 18
- Pain due to metastatic cancer of sufficient severity to warrant the use of opioids
- Normal haematologic, hepatic and renal function
- Mentally and physically competent to comply
- Informed consent

Exclusion criteria

- Undergoing active cancer treatment
- Receiving pain control other than analgesic medications (e.g. radiation therapy, nerve block)
- Inability to take oral medication
- Inability to tolerate morphine
- Requiring regular parenteral analgesics for pain control

Population

- 20 adult patients with cancer related pain. All were using opiates (morphine/ oxycodone/ hydromorphone/ anileridine) before the study.

Interventions

Titration phase established the daily morphine dose required for adequate pain control.

- SR morphine every 12 hours at 8am and 8pm

Or

- IR morphine every 4 hours at 8am, 12pm, 4pm and 8pm

Morphine doses were adjusted individually to obtain pain control with the least side effects

Outcomes

Pain intensity (10cm VAS ranging from "no pain" to agonising pain")
Supplemental IR morphine
Side effects (0 = none; 1 = mild; 2 = moderate; 3 = severe)

Results

Pain intensity (mean VAS cm ranging from "no pain" to agonising pain") (SDs were not presented)

Day	SR morphine	IR morphine
1	1.3	1.2
2	1.1	1.2
3	1.2	1.5
4	1.4	1.5
5	1.3	1.2
6	1.4	1.3
7	1.2	1.8
1-7	1.3	1.4

There were no significant differences between the two groups in terms of pain intensity.

Supplemental IR morphine

SR morphine		IR morphine	
Number requiring supplementary morphine	Mean supplemental dose (SD)	Number requiring supplementary morphine	Mean supplemental dose (SD)
9	15.4mg (18.4mg)	10	23.7mg (23.8)

There was no statistically significant difference between IR and CR in terms of the requirement for supplemental morphine

Side effects (SDs were not presented)

(0 = none; 1 = mild; 2 = moderate; 3 = severe)

Side effect	SR morphine	IR morphine
Nausea	0.23	0.39
Vomiting	0.10	0.18
Constipation	0.67	0.35
Drowsiness	0.93	1.08
Dizziness	0.53	0.45
Restlessness	0.46	0.49
Agitation	0.54	0.63
Tiredness	0.85	1.12
Dryness of mouth	0.72	0.94

There were no significant differences between the two groups in terms of side effects.

General comments

- The study was double blinded (maintained by the double dummy technique)
- Randomisation was conducted by the pharmaceutical company using a randomisation table
- Eight patients failed to complete. ITT analyses not conducted.

Citation: Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. et al. (1993). Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *Journal of Clinical Oncology, 11,* 967-972.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: USA
Aim: The study was performed with the following objectives: (1) to compare the analgesic efficacy of immediate-release morphine (IRM) administered every 4 hours and sustained-release morphine (SRM) administered every 12 hours orally to outpatients with severe pain due to cancer; (2) to evaluate the frequency and time occurrence of breakthrough pain; and (3) to assess the frequency of symptoms or side effects associated with oral morphine.

Inclusion criteria

- Age ≥ 18
- Pain due to advanced cancer
- Outpatients being cared for in their homes
- Pain that required treatment with a stable daily dose of at least 60mg of IRM
- Life expectancy of longer than 1 week, but less than 6 months

Population

37 adult patients with cancer related pain. Participants were receiving IRM every 4 hours at baseline.

Interventions

On day one of the study, all patients received their usual daily doses of IRM and baseline data were collected. On days 2 and 3 patients received:

- Active SRM 30mg every 12 hours and placebo oral solution every 4 hours

Or

- Active IRM 20mg/mL every 4 hours and placebo tablets identical to SRM every 12 hours

On day 4 patients were crossed over to alternate treatment, which they received for the subsequent 3 days (days 4-6). The baseline dose range of morphine was 60-360mg/day and for SRM it was 60 – 300mg/day

Outcomes

- Analgesic efficacy (at 2pm and 9pm on days 1-6 using a 100 mm VAS. A difference of 25mm between VAS scores was specified pre-study as indicating clinically meaningful effect on days 3 and 6)
- Breakthrough pain
- Side effects (once a day, relating to the previous 24 hours)

Results

Analgesic efficacy (mean VAS rating on 100mm scale)

	Time			
	Noon	4pm	9pm	Overall
IRM baseline	21.71 ± 3.97	26.79 ± 5.07	25.04 ± 5.09	24.51 ± 2.72
IRM	20.00 ± 4.07	19.40 ±4.15	20.08 ± 4.33	20.00 ± 2.42
SRM	18.80 ± 3.67	18.20 ± 4.07	22.50 ± 4.30	19.80 ± 2.32

There were no statistically significant differences at any measurement time point.

Breakthrough pain

	Number of patients experiencing breakthrough pain				
	No breakthrough pain during treatment with SRM or IRM	Breakthrough pain during both SRM and IRM	Breakthrough pain during IRM but not SRM	Breakthrough pain during SRM but not IRM	P
No. patients (N = 34)	29	2	0	3	0.25

Side effects (mean VAS scores)

	Time		
Variable	Noon	4pm	9pm
IRM	9.8 ± 3.38	10.9 ± 3.76	15.8 ± 5.04
SRM	10.3 ± 2.94	9.5 ± 2.93	9.3 ± 3.01
Sedation			
IRM	34.4 ± 6.15	30.1 ± 5.63	40.0 ± 6.41
SRM	26.3 ± 5.61	29.6 ± 5.48	40.03 ± 6.23
Anxiety			
IRM	28.3 ± 5.98	26.9 ± 5.90	27.5 ± 5.76
SRM	27.5 ± 5.01	23.8 ± 4.89	25.9 ± 5.28
Depression			
IRM	22.9 ± 5.17	20.8 ± 5.01	25.2 ± 5.36
SRM	29.1 ± 4.85	21.3 ± 4.41	22.8 ± 4.71

There were no statistically significant differences between groups in terms of side effects

General comments

- Randomisation and allocation concealment were sufficient
- The study was double blinded (maintained by the double dummy technique)
- 25/34 (74%) patients who completed the study were female
- Mean age was 59
- ITT analyses were not performed
- Three patients did not complete the six day study (two chose to withdraw; one died on day 5)
- Demographic characteristics were equivalent in each group at baseline

Citation: Gillette, J. F. (1997). Double-blind crossover clinical and pharmacokinetic comparison of oral morphine syrup and sustained release morphine sulfate capsules in patients with cancer-related pain. *Clinical Drug Investigation, 14,* 22-27.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: France
Aim: To evaluate the efficacy and bioavailability of a new sustained-release (SR) morphine sulphate formulation

Inclusion criteria

- Age ≥ 18 years
- Normal renal and hepatic function
- End stage cancer

Exclusion criteria

- Oncological treatment within 4 weeks of study entry
- Severe nausea or vomiting
- Contraindications to opiate drugs

Population
35 male and female adults with advanced cancer and severe pain. Pain was not controllable by step 2 analgesics (according to WHO criteria)

Interventions

- SR morphine capsules every 12 hours (8am and 8pm)

Versus

- Immediate-release (IR) morphine syrup every 4 hours (4am, 8am, 12pm, 4pm, 8pm, 12am)

6 day treatment regimen
A stabilisation period was conducted to achieve satisfactory pain relief with IR morphine (up to 300mg/day)

Outcomes

- Pain intensity (assessed 4 times daily at 10am, 2pm, 6pm, 10pm) on a 100mm VAS)
- Adverse events
- Side effects
- Pharmokinetics

Results
Pain intensity (assessed 4 times daily at 10am, 2pm, 6pm, 10pm) on a 100mm VAS)
Mean ± SD

	SR morphine	IR morphine
Baseline	83.0 ± 14.3mm	82.4 ± 11.4mm
Mean over study period	10.1 ± 2.1mm	10.5 ± 2.4mm

There were no significant differences between groups in terms of pain scores.

Adverse events (no. patients (%))

	SR morphine	IR morphine
Patients with ≥ 1 AE	25 (93%)	25 (93%)
Withdrawal because of AE	0 (0%)	0 (0%)

There were no significant differences between groups in terms of adverse events.

Side effects (no. patients (%))

	SR morphine	IR morphine
Constipation	14 (52%)	16 (60%)
Nausea	11 (41%)	11 (41%)
Dry mouth	21 (78%)	20 (74%)
Somnolence	15 (55%)	14 (52%)
Dizziness	1 (4%)	2 (7%)
Agitation	6 (22%)	3 (11%)
Euphoria	4 (15%)	2 (7%)
Pruritus	4 (15%)	5 (19%)

Nightmares	3 (11%)	4 (15%)
Urinary retention	1 (4%)	1 (4%)

There were no significant differences between groups in terms of side effects.

General comments

- Method of randomisation and allocation concealment was unclear
- Double blind
- Placebo used

Citation: Hanks, G. W., Twycross, R. G., Bliss, J. M., Hanks, G. W., Twycross, R. G., & Bliss, J. M. (1987). Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. *Anaesthesia, 42,* 840-844.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: UK
Aim: To compare 4 hourly aqueous morphine sulphate and twice daily sustained-release morphine tablets.

Inclusion criteria

- Patients with advanced cancer admitted to hospital based continuing care
- Pain that was controlled by 4 hour aqueous morphine sulphate in aqueous solution
- Received the same dose of morphine for at least 7 days

Exclusion criteria

- Patients who were too or confused
- Pain not stable

Population

- 27 patients male and female adults with cancer related pain. All participants had their pain controlled by 4 hour aqueous morphine sulphate in aqueous solution at baseline

Interventions

- SR morphine tablets twice a day (10am and 10pm)

Versus

- Immediate-release (IR) aqueous morphine (6am, 10am, 2pm, 6pm, 10pm, and for some patients 2am)

Outcomes

- Pain intensity (0 – 100 VAS scale)
- Side effects (0 – 100 VAS)

Results

Pain intensity

	SR morphine	IR morphine
Initial	80.2 (5.0)	86.1 (2.8)
Final	75.3 (7.2)	82.4 (4.8)
Median change (95% CI)	0.0 (-55.0 - 70.0)	0.0 (-51.0 - 60.0)
P	0.948	

Side effects

	Alertness		Nausea		Mood		Sleep		Appetite	
	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR
Initial	78.8 (4.1)	51.7 (8.0)	86.9 (3.1)	84.8 (3.6)	15.2 (4.2)	14.9 (4.6)	28.6 (6.7)	16.3 (4.3)	24.9 (7.2)	19.1 (6.5)
Final	75.2 (6.0)	81.7 (4.3)	85.8 (5.1)	87.8 (3.7)	14.5 (4.8)	18.5 (5.4)	13.6 (3.1)	22.3 (4.5)	32.0 (8.0) 32.0 (8.0)	28.8 (8.4)
Median change (95% CI)	-0.5 (-8.1 - 15.3)	-20.5 (-46.3 - -13.6)	0.5 (-9.2 – 11.5)	-2.5 (-11.5 – 5.5)	1.0 (-4.1 – 5.6)	-0.5 (-10.2 – 3.1)	6.5 (3.3-26.8)	-2.0 (-15.8 – 3.7)	0.0 (-17.7 – 3.4)	1.0 (24.1 ± 4.7)
P	0.007		0.339		0.266		0.017		0.938	

That is, IR morphine seemed to be associated with improved alertness while SR morphine seemed to be associated with improved quality of sleep, but it should be noted that the groups differed at baseline on these measures.

General comments

- Method of allocation and concealment were unclear
- Only 18/27 (67%) completed the study. Reasons for withdrawals were fully reported. No ITT analysis.
- Double blinded

Citation: Kaplan, R., Parris, W. C., Citron, M. L., Zhukovsky, D., Reder, R. F., Buckley, B. J. et al. (1998). Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *Journal of Clinical Oncology, 16,* 3230-3237.

Design: RCT (parallel groups)
Country: USA
Aim: To compare the efficacy, acceptability of therapy, and safety of sustained-release (SR) oxycodone tablets with immediate-release (IR) oxycodone tablets in patients with cancer related pain.

Inclusion criteria

- Being treated with a strong single entity opioid or 10 or more tablets per day of a fixed dose opioid/non-opioid analgesic
- Receiving a stable opioid dose
- Stable coexistent disease
- Written informed consent

*After the study had begun, these criteria eliminated by an amendment to facilitate enrolment into the study

Population

- 164 male and female adults with cancer pain (108 before protocol amendment; 72 after protocol amendment)

Interventions

- IR oxycodone

Versus

- SR oxycodone

The original protocol did not allow dose titration or use of supplemental analgesics for breakthrough pain. Patients whose pain was not effectively controlled at the initial oxycodone dose calculated from previous opioid use were discontinued from the study. The protocol was subsequently amended to include open label titration with IR oxycodone before participants were randomised to double blind treatment, and the use of IR oxycodone 5mg tablets as supplemental analgesic. Supplemental doses could be taken no more frequently than every 4 hours.

Outcomes

- Dose administered
- Pain intensity
- Acceptability of therapy
- Discontinuation
- Side effects

Results

Dose administered (mean)

SR oxycodone (n=78)	IR oxycodone (n = 82)
127mg (range 40-640mg)	114mg (range 20 – 400mg)

Pain intensity (average of daily assessments for all 5 days)

SR oxycodone (n=78)	IR oxycodone (n = 82)
1.3±0.1	1.3±0.1

*NB values were identical

Acceptability of therapy

	SR oxycodone (n=78)	IR oxycodone (n = 82)
Baseline	3.5±0.1	3.5±0.1
End of study	3.2±0.1	3.2±0.1

*NB values were identical

Discontinuation

Reported separately for those who entered study before versus after amendment of the protocol

	Titration and rescue allowed (n = 55)				No titration or rescue (n = 105)			
	SR (n = 28)		IR (n = 27)		SR (n = 50)		IR (n = 55)	
	No.	%	No.	%	No.	%	No.	%
Lack of acceptable pain control	1	4	5	19	17	34	17	31
Adverse event	2	7	3	11	4	8	7	13
Other reason	3	11	2	7	6	12	5	9
All reasons	6	21	10	37	27	54	29	53

Side effects

Side effects	SR oxycodone (n=78)			IR oxycodone (n = 82)		
	Patients		No. of reports	Patients		No. of reports
	No.	%		No.	%	
Nausea	14	18	16	21	26	30
Somnolence	14	18	16	17	21	18
Constipation	9	12	9	17	21	17
Vomiting	8	10	11	14	17	23
Dizziness	5	6	6	11	13	14
Sweating	4	5	5	3	4	3
Asthenia	3	4	4	8	10	9
Nervousness	3	4	3	5	6	5
Dry mouth	3	4	3	5	6	5
Pruritus	2	3	3	4	5	4
Insomnia	2	3	2	4	5	4
Headache	0	0	0	6	7	7
Anxiety	0	0	0	4	5	4

Overall significantly fewer adverse events were reported for CR oxycodone compared with IR oxycodone (p = 0.006)

There were significantly fewer adverse events associated with the digestive system in the SR oxycodone group than the IR oxycodone group (p = not reported)

Fewer patients in the SR oxycodone group reported headache compared with the IR oxycodone group (p = 0.029).

General comments

- Double blind
- Unclear methods of sequence generation and allocation concealment
- Exclusion criteria were eliminated mid way through the study by an amendment to facilitate enrolment into the study
- The study protocol was altered mid way through the study to include open label titration with IR oxycodone before participants were randomised to double blind treatment, and the use of IR oxycodone 5mg tablets as supplemental analgesic.
- 96% of patients took ≥ 90% of doses of study medication

Citation: Klepstad, P., Kaasa, S., Jystad, A., Hval, B., Borchgrevink, P. C., Klepstad, P. et al. (2003). Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain, 101,* 193-198.

Design: RCT (parallel groups)
Country: Norway
Aim: To compare the efficacy of oral immediate-release (IR) morphine titration and sustained-release (SR) morphine

titration in a randomised double blind controlled study

Inclusion criteria

- Age ≥ 18 years
- Pain despite ongoing treatment for weak to mild pain
- Chronic cancer pain

Exclusion criteria

- Weak opioids not titrated to maximal recommended dose
- Morphine intolerance
- Decreased gastrointestinal uptake of oral medications
- Scheduled transfer from hospital

Population

- 40 male and female adults with cancer related pain despite treatment with opioids for mild to moderate pain

Interventions

- SR morphine tablets once daily

Versus

- IR morphine tablets every 4 hours

Outcomes

- Time to acceptable pain relief
- Pain intensity (daily average for the previous 24 hours on a 100mm VAS anchored at one end by "no pain" and at the opposite end by "unbearable pain")
- Side effects (VRS where 1 = not at all; 2 = some; 3 = severe; 4 = very severe)
- Health related quality of life (at end of study using QLQ-C30)

Results

Days to acceptable pain relief

Mean (95% CI)

SR morphine (n = 19)	IR morphine (n = 15)
1.7 (1.7 – 2.0)	2.1 (1.4 – 2.7)

There was no statistically significant difference between groups in terms of time to acceptable pain relief.

Pain intensity (daily average for the previous 24 hours on a 100mm VAS)

Mean (95% CI)

SR morphine (n = 19)	IR morphine (n = 15)
22 (14 – 29)	26 (17 – 36)

There was no statistically significant difference between groups in terms of pain intensity.

Side effects (intensity of symptoms before and after titration on a VRS where 1 = not at all; 2 = some; 3 = severe; 4 = very severe)

Mean (95% CI)

	Baseline		After titration	
	SR	IR	SR	IR
Nausea	1.9 (1.4-2.4)	1.6 (1.2-1.9)	1.6 (1.3-1.9)	1.6 (1.3-2.0)
Tiredness	2.5 (2.2-2.9)	2.6 (2.2-3.0)	1.9 (1.5-2.2)	2.4 (2.0-2.8)
Constipation	2.1 (1.5-2.6)	1.7 (1.2-2.2)	1.9 (1.4-2.4)	1.7 (1.2-2.2)
Appetite	2.6 (2.0-3.1)	2.4 (1.8-3.0)	2.3 (1.8-2.7)	2.4 (1.9-2.9)
Vertigo	1.3 (1.0-1.5)	1.4 (1.0-1.8)	1.4 (1.1-1.7)	1.5 (1.1-1.8)
Lack of sleep	2.2 (1.6-2.8)	2.0 (1.4-2.6)	1.6 (1.1-2.0)	1.3 (1.0-1.5)

Patients titrated with IR morphine reported significantly more tiredness at the end of titration. There were no other significant differences between the two groups in terms of side effects.

Health related quality of life (before and after titration; scores range from 1-100, higher scores indicate better functioning)

Mean (95% CI)

	Before titration		After titration	
	IR	SR	IR	SR
Physical function	35 (22-48)	48 (34-63)	35 (22-49)	46 (29-62)

Role function	17 (5-28)	33 (19-47)	15 (0.3-30)	30 (13-46)
Emotional function	78 (69-87)	70 (61-79)	73 (62-85)	67 (57-77)
Cognitive function	70 (58-81)	59 (45-74)	68 (53-82)	74 (62-87)
Social function	49 (33-65)	43 (27-60)	46 (25-66)	44 (28-61)
Quality of life	44 (34-55)	37 (25-50)	42 (34-50)	44 (35-53)

There were no statistically significant differences between groups in terms of health related quality of life.

General comments

- Double blind (using the double dummy technique)
- Methods of randomisation unclear.
- Allocation concealment adequate

Citation: Knudsen J, Mortensen SM, Eikard B, & Henriksen H. Slow-release morphine tablets compared with conventional morphine tablets in the treatment of cancer pain. Ugeskrift for Læger 147; 780-4. 1985.

Design: Randomised, double-blind/double-dummy, cross-over study
Country:
Aim: To compare immediate-release morphine tablets (IRM) to sustained-release morphine tablets (SRM) in patients with moderate-severe cancer pain.

Inclusion criteria
Patients with ≥ 7 days of well-functioning treatment with IRM in constant 4-hourly dosing for moderate-severe pain from metastatic/invasive cancer which was not rapidly progressing. The patients also had to be judged physically and psychologically able to maintain a fixed dosage schedule and to complete questionnaires at fixed time points throughout a 2-week period.

Exclusion criteria
Intercurrent disease or occurrence of moribund condition

Population
N = 18 (2 of whom dropped out), 10 females, age range 39-66 years

Interventions
2 weeks duration (1 week of each treatment) - Same 24-hour dose was given of each treatment
IRM: 4-hourly tablets
SRM: 12-hourly tablets

Outcomes
Pain, sedation, side effects, patient preference

Results
Pain at individual time points (pain measured 2-hourly 7 times per day) and in total: IRM = SRM
Pain at each of the 7 days, and days 1-3 and 5-7 combined : IRM = SRM
Sedation at individual time points or days and days 5-7 combined: IRM = SRM
Sedation at days 1-3 combined: IRM < SRM (p < 0.02)
Side-effects: Nausea: N = 5 and 6 for SRM and IRM, respectively. Vomiting: N = 2 and 3 for SRM and IRM, respectively.
Dizziness: N = 3 and 2 for SRM and IRM, respectively.
Patient preference: N = 3 indicated that they preferred SRM, N = 8 preferred IRM and N = 5 preferred both equally.

General comments
Published in Danish
Not first-line treatment
Unclear allocation concealment

References of Included Studies (For systematic reviews): NA

Citation: Levy, M. H., Fitzmartin, R., & Reder, R. (1993). Comparison of immediate versus controlled release morphine (MS Contin) in the long-term management of cancer-related pain [abstract]. *Proceedings of the American Society of Clinical Oncology, 12*, 455 **(Abstract)**

Design: RCT (parallel groups)
Country: UK
Aim: To compare the use of immediate-release (IR) morphine tablets to sustained-release (SR) morphine tablets in the

long term management of pain in patients with advanced cancer

Inclusion criteria
- Cancer related pain

Population
- 65 adults with cancer related pain

Interventions
- SR morphine tablets

Versus
- IR morphine tablets

(no further details reported)

Outcomes
- Pain intensity
- Side effects
- Adverse events

Results
Pain
Pain intensity was mild in both groups (data not reported)
Side effects
Side effects were similar in both groups (data not reported)
Adverse events
Three reported: severe confusion (SR and IR); severe hypotension (SR).

General comments
- Abstract only
- Open label
- Method of randomisation and allocation concealment unclear
- Number of days in the study ranged from 1-608. 44/65 (68%) completed at least 4 weeks, and the primary analysis was based on this period

Citation: MacDonald, N., Bruera, E., Michaud, M., Brennels, C., Tennant, A., Walsh, T. D. et al. (1987). A double-blind, cross-over comparison between slow-release morphine (SRM) and short acting morphine (SAM) in the treatment of cancer pain. *Proceedings of the Annual Meeting of the American Society of Clinical Oncology* **(Abstract)**

Design: Randomised, double-blind, cross-over study (Abstract)
Country: Canada
Aim: To determine whether a sustained-release (SR) morphine preparation could adequately replace a less convenient formulation

Inclusion criteria
- Advanced cancer
- Receiving narcotics for the treatment of stable cancer pain

Exclusion criteria
Not reported

Population
- 28 patients with cancer related pain

Interventions
- SR morphine every 12 hours

Versus
- Immediate-release (IR) morphine every 4 hours in an equivalent daily dose

Outcomes
- Pain intensity
- Supplementary morphine
- Side effects

Results

	Baseline (mean)	SR morphine (mean)	IR morphine (mean)
Pain intensity at noon	20 ± 25	26 ± 21	18 ± 16
Pain intensity at 4pm	26 ± 22	22 ± 20	17 ± 16
Pain intensity at 9pm	25 ± 18	25 ± 20	19 ± 15
Number of supplemental doses of morphine	.30 ± .56	.58 ± .91	.33 ± .51
Sleeplessness	35 ± 25	32 ± 23	32 ± 20
Nausea	12 ± 15	8 ± 9	8 ± 8
Depression	14 ± 19	11 ± 15	10 ± 11
Anxiety	20 ± 20	15 ± 15	12 ± 11

There were no statistically significant differences between the two groups

General comments

- Abstract only
- Unclear whether the study was blinded
- Method of randomisation and allocation concealment was unclear

Citation: Panich, A., & Charnvej, L. (1993). Comparison of morphine slow release tablet (MST) and morphine sulphate solution (MSS) in the treatment of cancer pain. *Journal of the Medical Association of Thailand, 76,* 672-676.

Design: Randomised, single-blind (assessor) crossover study without placebo-control
Country: Thailand
Aim: To compare the effect of oral morphine, morphine sulphate sustained-release (SR) tablets and morphine sulphate solution for the treatment of pain in cancer patients

Inclusion criteria

- Cancer patients referred to a pain clinic

Exclusion criteria

- Unconscious
- Unable to speak

Population
23 male and female adults with severe cancer related pain

Interventions

- SR morphine tablets (30mg) every 12 hour

Versus

- Immediate-release (IR) morphine solution every (5-10mg) 4 hours

Cross-over design. Each phase was 7 days long.
Supplemental morphine available
At the end of the study patients were prescribed their preferred medication

Outcomes

- Pain intensity (measured at 8am and 4pm everyday using a 10cm VAS, a pain rating scale administered by a nurse (0 = no pain; 1 = mild; 2 = moderate; 3 = severe)
- Sleep duration
- Side effects
- Patient preference

Results
Pain intensity (mean ± SD)

	Before	Day 4	Day 5	Day 6	Day 7
SR					
VAS	5.9 ± 1.3	3.5 ± 2.0	3.3 ± 1.9	3.3 ± 2.1	3.2 ± 2.0
Nurse rating	2.4 ± 0.5	1.4 ± 0.9	1.4 ± 0.8	1.4 ± 0.7	1.3 ± 0.8
IR					
VAS	5.9 ± 1.3	3.1 ± 1.8	3.0 ± 1.7	2.9 ± 1.9	2.8 ± 1.9
Nurse rating	2.4 ± 0.5	1.4 ± 0.7	1.4 ± 0.7	1.2 ± 0.7	1.2 ± 0.7

There were no significant differences between groups in terms of pain scores.

Sleep duration

	Before	Day 4	Day 5	Day 6	Day 7
SR					
Daytime	3.3 ± 1.1	4.2 ± 1.5	4.1 ± 1.3	4.1 ± 1.3	4.2 ± 1.3
Night time	5.6 ± 1.7	6.9 ± 1.4	7.2 ± 1.3	7.2 ± 1.3	7.3 ± 1.1
IR					
Daytime	3.3 ± 1.1	4.3 ± 1.2	4.3 ± 1.3	4.4 ± 1.3	4.3 ± 1.3
Night time	5.6 ± 1.7	7.1 ± 1.7	7.3 ± 1.3	7.4 ± 1.4	7.5 ± 1.1

There were no significant differences between groups in terms of sleep duration.

Side effects

Side effect	SR Cases (%)	IR Cases (%)
Nausea & vomit	16 (32.6 %)	17 (34.7 %)
Constipation	21 (42.8 %)	16 (32.6 %)
Stupor	3 (6.1 %)	6 (12.2 %)
Dizziness	19 (38.8 %)	11 (22.45 %)
Anorexia	0 (0 %)	0 (0 %)
Itching	1 (2.0 %)	1 (2.0 %)
Tight in chest	2 (4.8 %)	0 (0 %)

There were no significant differences between groups in terms of side effects.

Patient preference

Chose SR: 14/49 (29%)

Chose IR: 35/49 (71%)

The difference between groups was significant ($p = 0.0002$). It is worth noting that 66% of patients were ENT patients who had difficulty swallowing tablets.

General comments

- Method of randomisation and allocation concealment was unclear
- Not placebo-controlled
- Single blind (assessor)
- 24/73 (33%) withdrew from the study. Reasons for drop-outs was fully reported.

Citation: Parris, W. C., Johnson, B. W., Jr., Croghan, M. K., Moore, M. R., Khojasteh, A., Reder, R. F. et al.,. (1998). The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. *Journal of Pain & Symptom Management, 16*, 205-211.

Design: RCT (parallel groups)
Country: France
Aim: To compare the effectiveness and safety of sustained-release (SR) oxycodone tablets with immediate-release (IR) oxycodone tablets in patients with chronic cancer pain

Inclusion criteria

- Age ≥ 18 years
- Cancer patients receiving 6 to 12 tablets or capsules a day of fixed-combination analgesics (opioid/non-opioid) for cancer-related pain
- Stable coexistent disease
- Written informed consent

Exclusion criteria

- Pain not already acceptably controlled
- Surgery or radiotherapy in prior 10 days
- Anticipated radiotherapy or surgery during study period
- Compromised functioning of a major organ system
- Receiving non-opioid analgesics (concomitant non-analgesic therapies were allowed during study)

Population

- 111 male and female adults with cancer pain

Interventions

- 30mg of SR oxycodone tablets every 12 hours daily for 5 days

Versus

- 15mg of IR oxycodone four times daily for 5 days

Outcomes

- Pain intensity (rated in a daily diary in the morning (overnight pain), midday (morning pain rating), evening (afternoon pain), and bedtime (evening pain) on a four point categorical (CAT) scale (0 = none; 1 = slight; 2 = moderate; 3 = severe)
- Acceptability (rated on a 5 point CAT scale: 1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent)
- Discontinuation rates
- Adverse events (assessors contacted patients daily by telephone and recorded information about adverse events and changes in condition daily)

Results

Pain intensity (average of the 4 CAT scale ratings on each study day)

	SR (mean ± SE)	IR (mean ± SE)
Mean baseline pain scores	1.5 ± 0.1	1.3 ± 0.1
Overall mean pain intensity scores (treatment completers)	1.4 ± 0.1	1.1 ± 0.1

A graph presents the mean daily scores. It was not of sufficient quality to enable accurate extraction of the data. There were no statistically significant differences between the CR and IR groups in terms of pain intensity ($P > 0.05$).

Acceptability

There were said to be no significant differences between treatment groups. Data was not reported. A graph presents the results, but it is not possible to extract accurate data. Mean acceptability scores by day were fair to good throughout the study period.

Discontinuation rates

37% of patients discontinued the 5-day study. There was no significant difference between treatment groups. Data was not reported.

Adverse events

Number of patients reporting at least one adverse event (considered by the investigators to be at least possibly related to treatment)

	SR	IR
At least one adverse event	36/52 (69%)	36/51 (70%)

Leaving the study due to adverse event(s)

	SR	IR
Leaving study due to adverse event(s) (%)	4/52 (8%)	7/51 (14%)

No patients died during the study

	Cancer patients	
Side effect, n (%)	**SR n = 51**	**IR n = 52**
Nausea	11 (20)	13 (24)
Somnolence	13 (24)	12 (22)
Dizziness	8 (15)	10 (19)
Constipation	12 (22)	10 (19)
Vomiting	5 (9)	11 (20)
Pruritus	7 (13)	5 (9)

Headache	7 (13)	3 (6)
Dry mouth	4 (7)	3 (6)
Sweating	1 (2)	5 (9)
Abdominal pain	3 (6)	1 (2)
Insomnia	3 (6)	1 (2)

There were no statistically significant differences between the two groups in terms of the incidence of adverse events, although there was a trend toward less nausea, vomiting and sweating in patients receiving SR oxycodone.

General comments

- This was a double blind study
- 94% of patients treated were at least 95% compliant
- Many of the outcomes are reported in insufficient detail to allow data extraction

Citation: Poulain, P., Krakowski, I., Lakdja, F., Maynadier, J., Petot, P., Salamagne, M., Hauseux, P., Saudubray, F., Bonny, N., and Lecheynne, J. [French multicentre therapeutic trial of slow-release morphine sulfate (Moscontin) in the treatment of neoplasic pain]. SO: Therapie 45[4], 364. 1990.

Design: Open-label, randomised, cross-over study (Abstract)
Country: France
Aim: to compare immediate-release morphine (IRMS) to sustained-release morphine (SRMS) for the treatment of pain in cancer patients.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population
N = 84

Interventions
IRMS: 2 successive treatment every 4 hours
SRMS: 2 successive treatments every 12 hours

Outcomes
Patient preference, pain control, side effects.

Results
N = 6 excluded due to worsening condition, treatment intolerance, and radiotherapy.
N = 78 in the analysis.

Patient preference: N = 10 preferred IRMS, N = 59 preferred SRMS, N = 8 did not indicate preference.
Side effects: IRMS = SRMS. > 50% of all patients experienced drowsiness and constipation.
Morphine dose necessary to achieve stable state of analgesia: Mean SRMS is 10 mg lower per day than IRMS.

General comments
- Open label
- These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

References of Included Studies (For systematic reviews): NA

Citation: Ranchere, J. Y., Vedrenne, J., Esteve, M., Roquefeuil, B., Kong, A., Siou, D. et al. (1991). Slow release morphine suspension versus morphine sulfate tablet (MST): a multicentre study in cancer pain. *European Journal of Cancer, 27,* S286. **(Abstract)**

Design: Multicenter, randomised, double-blind/double-dummy, cross-over study
Country: France
Aim: To compare sustained-release (SR) morphine suspension with morphine sulphate tablets

Inclusion criteria
- Cancer related pain

Population
- 52 cancer patients

Interventions
- SR morphine tablets

Versus
- Immediate-release (IR) morphine suspension

(no further details reported)

Outcomes
- Pain (self reported)
- Quality of life (self reported)
- Adverse events (assessor rated)
- Patient preference

Results
Pain (self reported)
There was no significant difference between groups (data not reported)
Quality of life (self reported)
There was no significant difference between groups (data not reported)
Adverse events (assessor rated)
There was no significant difference between groups (data not reported)
Patient preference
There was no significant difference between groups (data not reported)

General comments
- Abstract only
- Double blind
- Method of randomisation and allocation concealment was unclear

Citation: Salzman, R. T., Roberts, M. S., Wild, J., Fabian, C., Reder, R. F., Goldenheim, P. D. et al.,. (1999). Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *Journal of Pain & Symptom Management, 18,* 271-279.

Design: RCT (parallel groups)
Country: USA
Aim: To determine whether patients with chronic pain could be titrated to stable pain control as readily with sustained-release (SR) as with an immediate-release (IR) formulation of oral oxycodone

Inclusion criteria
- Age ≥ 18 years
- Stable chronic pain not adequately controlled by prior analgesic therapy with or without opioids
- Written informed consent

Exclusion criteria
- Allergy or contraindication to opioid therapy
- History of substance abuse
- Patients receiving an opioid analgesic that could not be discontinued
- Cancer patients prescribed oral oxycodone at a total dose of more than 400mg/day
- Non-cancer patients prescribed oral oxycodone at a total rate of more than 80mg/day

Population
- Study 1: 48 male and female adults with cancer pain
- Study 2: 57 male and female adults with moderate to severe lower back pain despite analgesic therapy

Interventions
Two separate trials comparing:
- SR oral oxycodone (administered every 12 hours (8am and 8pm ± 1 hour))

Versus

- IR oral oxycodone (administered every 4 hours (8am, 2pm, 8pm and bedtime ± 1 hour)

For opioid naive patients, the starting dose was 20mg/day. The starting dose was titrated upward in each study to a limit of 400mg/day for cancer patients and to 80mg/day for non-cancer patients or until patients rated their level of pain intensity at no greater than "slight". Dose adjusted every 24 to 48 hours as necessary.
Supplemental analgesic was permitted as needed for control of breakthrough or incident pain

Outcomes

- Stable analgesia
- Time to stable analgesia
- Final mean daily dose
- Pain intensity
- Patient rated pain intensity on a four point categorical scale (0 = none; 1 = slight; 2 = moderate; 3 = severe) recorded in a daily diary and assessed at the clinic visit at end of titration period
- Time to stable pain control (rated as zero in patients meeting criteria for success in the first 48 hours). Among cancer patients, titration rated successful if pain stabilised within a maximum of 21 days; among non-cancer patients, the time limit was 10 days.
- Adverse events recorded in a daily diary and assessed at the clinic visit at end of titration period

Results Only results for the cancer patients are reported.

Proportion achieving stable analgesia

Cancer patients	
SR **n = 24**	**IR** **n = 24**
22 (92%)	19 (79%)

Time to stable pain control

Cancer patients	
SR **n = 24**	**IR** **n = 24**
1.6 ± 0.4	1.7 ± 0.6

There was no significant difference between groups in terms of time to stable pain control.

Pain intensity
(Mean decrease from baseline ± SE)

Cancer patients	
SR **n = 24**	**IR** **n = 24**
0.7 ± 0.2 (P = 0.01)	0.3 ± 0.2 (P = 0.14)

Final mean daily doses

Cancer patients	
SR **n = 24**	**IR** **n = 24**
104mg (SE = 20)	113mg (SE = 24)

Patient assessment of pain intensity at baseline and end of titration (0 = none; 1 = slight; 2 = moderate; 3 = severe)

	Cancer patients	
	SR **n = 19**	**IR** **n = 16**
Baseline	1.8 (0.2)	1.4 (0.2)
End of titration	1.1 (0.2)	1.1 (0.1)

Side effects (only those occurring in greater than 10% of patients in at least one of the 4 treatment groups)

	Cancer patients	
Side effect, n (%)	**SR** **n = 24**	**IR** **n = 24**
Somnolence	9 (37)	7 (29)
Nausea	7 (29)	5 (21)
Vomiting	5 (21)	3 (12)

Postural hypotension	5 (21)	4 (17)
Constipation	4 (17)	9 (37)
Pruritus	4 (17)	0 (0)
Confusion	3 (12)	2 (8)
Dry mouth	3 (12)	1 (4)
Dizziness	2 (8)	0 (0)
Nervousness	2 (8)	4 (17)
Asthenia	2 (8)	1 (4)
Headache	1 (4)	1 (4)

General comments

- Two studies were reported. Patients with cancer participated in one study; patients who had chronic, moderate to severe back pain (despite analgesic therapy) participated in the other
- Participants in both studies were predominantly white and female
- 91% of patients reported taking an opiate-containing medication(s) prior to study entry
- Most patients were converted to the study drug from a variety of fixed-combination or single entity opioid therapies
- This was an open-label study
- There were no significant differences between groups on demographic variables at baseline in either study
- Withdrawals were fully reported with reasons

Citation: Stambaugh, J. E., Reder, R. F., Stambaugh, M. D., Stambaugh, H., Davis, M., Stambaugh, J. E. et al.,. (2001). Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *Journal of Clinical Pharmacology*, *41*, 500-506.

Design: Randomised, double-blind, cross-over study
Country: USA
Aim: To evaluate the efficacy of oral sustained-release (SR) oxycodone, given as twice daily dosing, as compared with immediate-release (IR) oxycodone given twice a day in patients with cancer pain. The study was designed to (1) to determine if the clinical efficacy and achievable plasma concentrations of oxycodone in the SR form as seen in prior studies were comparable to the IR form (2) to confirm the doses of SR every 12 hours provided equivalent analgesia to doses of IR oxycodone given 4 times a day.

Inclusion criteria

- Age ≥ 18 years
- Moderate or severe cancer related pain
- Ability to take oral medication
- Informed consent

Exclusion criteria

- Requirement for greater than 240mg/day oral oxycodone equivalent for pain relief
- Primary tumor or metastatic disease in the brain
- Received chemotherapy within 3 days of study entry
- Substance misuse
- Severe cognitive impairment
- Compromised renal or hepatic function
- Received radiotherapy to the site of pain
- Hypersensitivity to oxycodone

Population

- 40 male and female adults with moderate or severe cancer related pain

Interventions
Consisted of three periods with a duration of less than 35 days: a titration period of 2 – 21 days followed by two crossover periods

(1) Initial open-label titration period to stabilise patients on IR oxycodone (4 times daily).
(2) Participants randomised to double blind treatment:

- Immediate release oxycodone

Versus

- Controlled release oxycodone

(3) Crossover at the same daily dose

Outcomes

- Global pain (over the past 24 hours) and current pain on a scale of 0-10 (0 = no pain; 10 = severe pain)
- Current pain relief (0 = no relief; 10 = complete relief)
- Global acceptability (over the past 24 hours) and current acceptability on a scale of 1-5 (1 = very poor; 2 = poor; 3 = fair; 4 = good; 5 = excellent)
- Side effects

Results

Global (over previous 24 hours) pain intensity (during double blind periods)

		End of double blind periods		
Global pain intensity Mean (SD)	Start of titration	IR oxycodone	SR oxycodone	P value
	6.0 (2.2)	2.8 (1.9)	2.7 (1.9)	0.8804

Current pain relief and plasma concentrations of oxycodone (during double blind periods)

	IR oxycodone		SR oxycodone		p-value
Time	Mean	SD	Mean	SD	
Current pain relief					
0.75-1.5 hours	6.8	3.3	6.9	3.6	0.8318
2-4 hours	7.6	3.0	8.1	2.8	0.3018
Plasma concentrations					
0 hours	32.9	29.7	38.7	36.0	0.1966
0.75-1.5 hours	50.4	39.0	38.0	41.0	0.1184
2-4 hours	51.0	40.8	41.9	51.0	0.3571

Side effects (during double blind periods)

	IR oxycodone (n = 31)			SR oxycodone (n = 30)		
	Number	%	Reports	Number	%	Reports
Nausea	4	13	4	3	10	3
Dizziness	3	10	3	3	10	3
Somnolence	3	10	5	2	7	4
Asthenia	2	6	2	2	7	2
Pruritus	1	3	1	2	7	2
Sweating	2	6	2	1	3	1
Constipation	1	3	1	1	3	1
Dry mouth	1	3	1	1	3	1
Nervousness	0	0	0	1	3	1
Vomiting	2	6	2	0	0	0
Total	10	32	21	10	33	21

General comments

- Method of sequence generation and allocation concealment unclear
- Double blind
- Opioids other than the study medication were prohibited
- 25% (10/40) discontinued the study. Reasons for drop-outs were fully reported
- Pain intensity scores and blood samples were obtained with 100% compliance from the 30 completers

Citation: Thirlwell, M. P., Sloan, P. A., Maroun, J. A., Boos, G. J., Besner, J. G., Stewart, J. H. et al. (1989). Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer, 63*, 2275-2283.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: Canada
Aim: To compare the pharmacokinetics and clinical efficacy of immediate-release (IR) morphine sulphate solution and sustained-release (SR) morphine sulphate tablets

Inclusion criteria

- Age ≥ 18 years
- Requiring oral opioid therapy for cancer related pain
- Mentally and physically competent to comply with therapeutic protocol
- Written informed consent

Exclusion criteria

- Hepatic or renal impairment
- Severe nausea and/or vomiting
- Uncontrolled pain requiring frequent parenteral morphine
- Scheduled to receive a course of chemotherapy or radiotherapy in the 7 days before or anytime during the trial

Population

- 23 male and female adults with cancer related pain. Some used regular opioid analgesics at baseline (unclear exactly how many)

Interventions

- SR morphine tablets every 12 hour

Versus

- IR morphine tablets every 4 hours

Cross-over design. Each phase was at least 5 days long.
Supplemental IR morphine for breakthrough pain
Opioid dose before the study dictated starting trial dose

Outcomes

- Pain intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe)
- Side effects
- Supplemental morphine
- Pharmacokinetics

Results

Pain intensity (mean)

SR morphine (n = 18)	IR morphine (n = 18)	P
0.55 ± 0.58	0.57± 0.63	0.85

Side effects (frequency)

	SR morphine (n = 18)	IR morphine (n = 18)
Nausea	3	3
Dizziness	3	3

There were no statistically significant differences between groups in terms of the frequency or severity side effects

Supplemental morphine (no. patients requiring extra dose)

SR morphine (n = unclear)	IR morphine (n = unclear)
3	3

General comments

- Double blind (using the double dummy technique)
- Method of allocation and concealment were unclear
- Reasons for withdrawals were fully reported
- ITT analyses were not performed

Citation: Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A., De, C. F., Ventafridda, V. et al. (1989). Clinical

observations on controlled-release morphine in cancer pain. *Journal of Pain & Symptom Management, 4*, 124-129.

Design: RCT (parallel groups)
Country: Italy
Aim: To conduct a clinical comparison between sustained-release (SR) morphine sulphate tablets and immediate-release (IR) morphine solution.

Inclusion criteria

- Advanced cancer patients

Exclusion criteria

- No strong narcotics in past month

Population

- 70 male and female adults with cancer related pain. Patients had not taken strong narcotics in the past month.

Interventions

- SR morphine tablets

Versus

- IR morphine solution

Depending on the analgesic response to previous treatments, initial doses of CR morphine varied from 20mg/day to a maximum of 120mg/day. Initial doses of IR morphine varied from a minimum of 24mg/day to a maximum of 144mg/day as 4% solution

Outcomes

- Pain intensity
- Drug dosage and dosing intervals
- Side effects

Results

Pain intensity

Mean daily pain scores were reported on a graph. Data could not be extracted.
The mean difference in pain score from day 1 to 14 was 19.4 in the IR group and 22.5 in the SR group. There was no significant difference between groups (p = not reported).

Drug dosage and dosing intervals

Mean daily dosages were reported on a graph. Data could not be extracted.
There was a non significant difference between mean dosages administered from day 1 – 14 (p = .20)

Side effects

Mean daily side effect scores were reported on a graph. Data could not be extracted.
The frequency of daily side effects was lower in patients on SR morphine than IR. These differences were significant for itching (p = .001), dry mouth (p = .001), drowsiness (p = .001), nausea (p = .001), vomiting (p = .001), headache (p = 0.01), constipation (p = .001). There were non-significant differences in terms of trembling and restlessness.

General comments

- An additional study of SR morphine was carried out concurrently. This was not an RCT
- The study was not blinded
- Method of allocation and concealment were unclear
- Only 32/70 (46%) completed the study
- Reasons for withdrawals were fully reported
- ITT analyses were not performed
- Results were not well reported

Citation: Walsh, T. D. (1985). Controlled study of oral slow-release morphine in pain due to advanced cancer. *Proceedings of the Annual Meeting of the American Society of Clinical Oncology* **(Abstract).**

Design: Randomised, double-blind/double-dummy, cross-over study
Country: UK
Aim: To compare the clinical analgesic efficacy and side effects of a new sustained-release morphine tablet given 12 hourly to immediate-release (IR) morphine.

Inclusion criteria

- Cancer related pain

Population
- 36 male and female adults with cancer related pain

Interventions
- SR morphine tablets 12 hourly

Versus
- IR morphine liquid formulation 4 hourly

Outcomes
- Pain
- Side effects

Results

Pain

Analysis by paired/unpaired t-tests and contingency tables revealed no significant differences in analgesic efficacy between the two preparations

Side effects

Analysis by paired/unpaired t-tests and contingency tables revealed no significant differences in side effects between the two preparations

General comments
- Abstract only
- Double blind
- Method of randomisation and allocation concealment was unclear

Citation: Walsh, T. D., MacDonald, N., Bruera, E., Shepard, K. V., Michaud, M., Zanes, R. et al. (1992). A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. *American Journal of Clinical Oncology, 15*, 268-272.

Design: Randomised, double-blind/double-dummy, cross-over study
Country: UK
Aim: To compare the safety and efficacy of sustained-release (SR) and immediate-release (IR) morphine in patients with advanced cancer

Inclusion criteria
- Cancer related pain

Exclusion criteria
- Two or more parenteral doses of morphine for breakthrough pain during the 24 hours of the baseline day
- Unstable fluctuating pain
- Unable to take regular oral medication

Population
- 33 male and female adults with cancer related pain. Patients were taking morphine at study entry.

Interventions
- SR morphine tablets 12 hourly

Versus
- IR morphine liquid formulation 4 hourly

Outcomes
- Pain (100mm VAS)
- Side effects

Results

Pain (100mm VAS)

Mean (SD)

	12pm	4pm	9pm	Overall
SR	27.78 (5.13)	20.63 (4.30)	26.06 (4.30)	24.82 (2.64)
IR	22.00 (4.75)	16.04 (3.25)	21.02 (3.44)	19.69 (2.23)

There were no statistically significant differences between groups in terms of pain scores.

Side effects

Mean (SD)

		12pm	4pm	9pm
Nausea	IR	9.0 (2.26)	12.9 (4.01)	5.8 (1.65)
	SR	10.4 (3.25)	9.3 (3.21)	9.9 (3.82)
Sedation	IR	33.6 (5.51)	38.5 (5.87)	37.3 (5.57)
	SR	35.6 (5.85)	33.4 (5.16)	39.1 (6.59)
Anxiety	IR	19.0 (4.05)	11.2 (2.93)	12.9 (3.15)
	SR	11.0 (3.10)	15.1 (4.24)	16.8 (5.03)
Depression	IR	12.2 (3.77)	8.4 (2.15)	9.3 (3.60)
	SR	12.4 (3.60)	13.0 (3.96)	11.0 (3.38)

There were no statistically significant differences between groups in terms of side effects.

General comments

- Double blind
- Double dummy technique used
- Method of randomisation and allocation concealment adequate

Citation: Xu, G. Z., Cai, Z. J., Li, T. D., Liu, A. G., Xie, G. R., Liu, S. M., Chen, C. H., Ma, Q. L., hou, J., Deng, Y. P., and Lu, X. X. [Clinical evaluation of analgesic effect of controlled release morphine sulphate tablets in patients with cancer pain]. SO: The Chinese Journal of Clinical Pharmacology 11[2], 88-97. 1995.

Design: RCT ((parallel groups; abstract)
Country: China
Aim: to compare immediate-release morphine sulphate (IRMS) with sustained-release morphine (SRMS) cancer patients with moderate-severe pain.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population

N = 262

Interventions

SRMS: 30 mg sustained-release oral morphine 12 hourly (N = 101) for 6 days.
SRMS: 60 mg sustained-release oral morphine 12 hourly (N = 58) for 6 days.
IRMS: 10 mg immediate-release oral morphine 4 hourly (N = 103) for 6 days.

Outcomes

Pain intensity difference, sum of pain intensity difference, pain relief, total pain relief, rate of pain relief over grade 2 and total analgesic score.

Results

"Clinical results showed that there was no significant difference between the two treatment groups" (p 97).

General comments

- Double-blind
- These data are only included in abstract form as the full article is published in Chinese. It is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

References of Included Studies (For systematic reviews): NA

Summary table of the results of the meta-analyses of IR v SR oxycodone of topic 2a

Side effect	Studies	Participants	Statistical method	Effect size (Risk Ratio) [95% CI]
Nausea	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.26]
Dizziness	3	311	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.35]
Drowsiness	3	311	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.52]
Vomiting	3	311	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.44]
Constipation	3	311	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.44, 1.12]
Pruritus	3	311	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.64, 3.18]
Dry mouth	3	311	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.47, 2.71]
Nervousness	2	208	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.20, 1.63]
Asthenia	2	208	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.18, 1.47]
Headache	3	311	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.16, 1.63]
Sweating	2	263	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.09, 4.19]

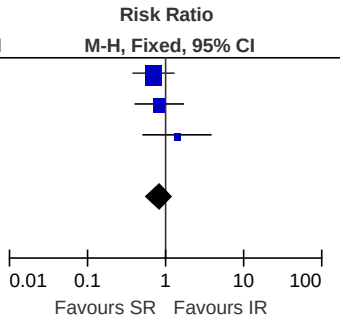
Forest plots of the results of review question 2a

Nausea

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	14	78	21	82	53.0%	0.70 [0.38, 1.28]
Parris et al. (1998)	11	52	13	51	34.0%	0.83 [0.41, 1.68]
Salzman et al. (1999)	7	24	5	24	13.0%	1.40 [0.52, 3.80]
Total (95% CI)		**154**		**157**	**100.0%**	**0.84 [0.55, 1.26]**
Total events	32		39			

Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%

Test for overall effect: Z = 0.85 (P = 0.39)

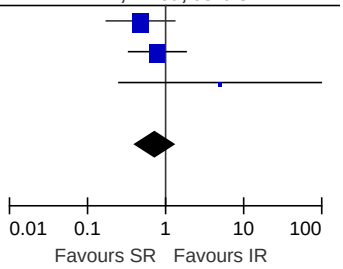


Dizziness

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	5	78	11	82	50.3%	0.48 [0.17, 1.31]
Parris et al. (1998)	8	52	10	51	47.4%	0.78 [0.34, 1.83]
Salzman et al. (1999)	2	24	0	24	2.3%	5.00 [0.25, 98.96]
Total (95% CI)		**154**		**157**	**100.0%**	**0.73 [0.40, 1.35]**
Total events	15		21			

Heterogeneity: Chi² = 2.30, df = 2 (P = 0.32); I² = 13%

Test for overall effect: Z = 1.01 (P = 0.31)

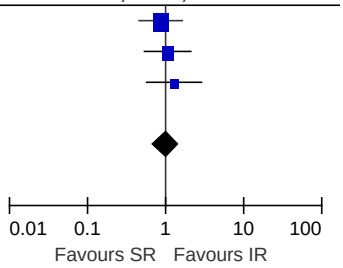


Drowsiness

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	14	78	17	82	46.4%	0.87 [0.46, 1.64]
Parris et al. (1998)	13	52	12	51	33.9%	1.06 [0.54, 2.10]
Salzman et al. (1999)	9	24	7	24	19.6%	1.29 [0.57, 2.89]
Total (95% CI)		**154**		**157**	**100.0%**	**1.01 [0.68, 1.52]**
Total events	36		36			

Heterogeneity: Chi² = 0.59, df = 2 (P = 0.75); I² = 0%

Test for overall effect: Z = 0.07 (P = 0.94)

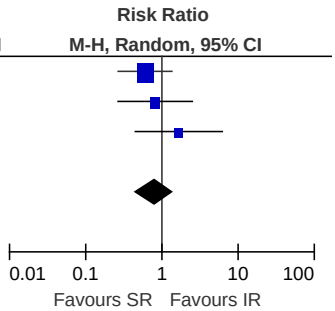


Vomiting

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaplan et al. (1998)	8	78	14	82	52.5%	0.60 [0.27, 1.35]
Parris et al. (1998)	5	52	6	51	27.5%	0.82 [0.27, 2.51]
Salzman et al. (1999)	5	24	3	24	20.0%	1.67 [0.45, 6.21]
Total (95% CI)		**154**		**157**	**100.0%**	**0.80 [0.45, 1.44]**
Total events	18		23			

Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%

Test for overall effect: Z = 0.74 (P = 0.46)

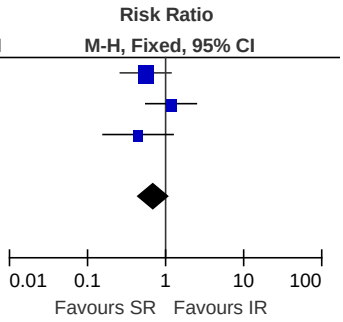


Constipation

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	9	78	17	82	46.5%	0.56 [0.26, 1.17]
Parris et al. (1998)	12	52	10	51	28.3%	1.18 [0.56, 2.48]
Salzman et al. (1999)	4	24	9	24	25.2%	0.44 [0.16, 1.25]
Total (95% CI)		**154**		**157**	**100.0%**	**0.70 [0.44, 1.12]**
Total events	25		36			

Heterogeneity: Chi² = 2.97, df = 2 (P = 0.23); I² = 33%

Test for overall effect: Z = 1.49 (P = 0.14)

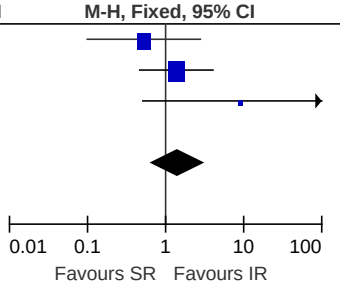


Pruritus

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	2	78	4	82	41.3%	0.53 [0.10, 2.79]
Parris et al. (1998)	7	52	5	51	53.4%	1.37 [0.47, 4.05]
Salzman et al. (1999)	4	24	0	24	5.3%	9.00 [0.51, 158.52]
Total (95% CI)		**154**		**157**	**100.0%**	**1.43 [0.64, 3.18]**
Total events	13		9			

Heterogeneity: Chi² = 2.96, df = 2 (P = 0.23); I² = 33%

Test for overall effect: Z = 0.87 (P = 0.38)

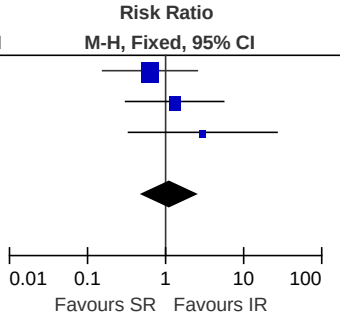


Dry mouth

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	3	78	5	82	54.7%	0.63 [0.16, 2.55]
Parris et al. (1998)	4	52	3	51	34.0%	1.31 [0.31, 5.55]
Salzman et al. (1999)	3	24	1	24	11.2%	3.00 [0.34, 26.84]
Total (95% CI)		**154**		**157**	**100.0%**	**1.13 [0.47, 2.71]**
Total events	10		9			

Heterogeneity: Chi² = 1.47, df = 2 (P = 0.48); I² = 0%

Test for overall effect: Z = 0.27 (P = 0.79)

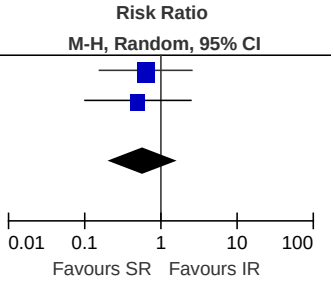


Nervousness

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaplan et al. (1998)	3	78	5	82	56.7%	0.63 [0.16, 2.55]
Salzman et al. (1999)	2	24	4	24	43.3%	0.50 [0.10, 2.48]
Total (95% CI)		**102**		**106**	**100.0%**	**0.57 [0.20, 1.63]**
Total events	5		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.30)

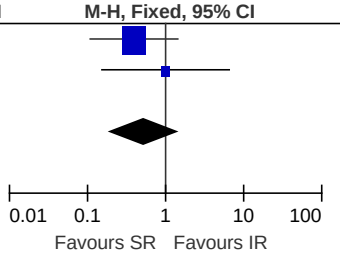


Asthenia

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kaplan et al. (1998)	3	78	8	82	79.6%	0.39 [0.11, 1.43]
Salzman et al. (1999)	2	24	2	24	20.4%	1.00 [0.15, 6.53]
Total (95% CI)		**102**		**106**	**100.0%**	**0.52 [0.18, 1.47]**
Total events	5		10			

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%

Test for overall effect: Z = 1.24 (P = 0.22)

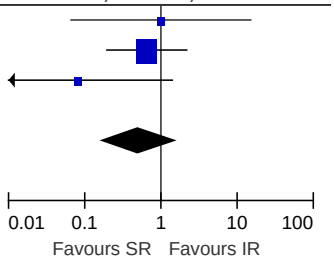


Headache

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaplan et al. (1998)	1	24	1	24	17.2%	1.00 [0.07, 15.08]
Parris et al. (1998)	4	52	6	51	67.2%	0.65 [0.20, 2.18]
Salzman et al. (1999)	0	78	6	82	15.6%	0.08 [0.00, 1.41]
Total (95% CI)		**154**		**157**	**100.0%**	**0.51 [0.16, 1.63]**
Total events	5		13			

Heterogeneity: Tau² = 0.15; Chi² = 2.24, df = 2 (P = 0.33); I² = 11%

Test for overall effect: Z = 1.14 (P = 0.26)

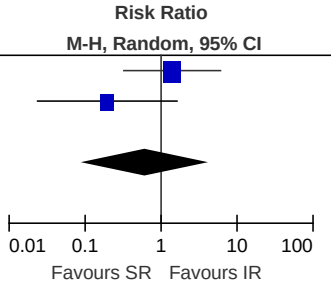


Sweating

Study or Subgroup	SR Events	SR Total	IR Events	IR Total	Weight	Risk Ratio M-H, Random, 95% CI
Kaplan et al. (1998)	4	78	3	82	57.6%	1.40 [0.32, 6.06]
Parris et al. (1998)	1	52	5	51	42.4%	0.20 [0.02, 1.62]
Total (95% CI)		**130**		**133**	**100.0%**	**0.61 [0.09, 4.19]**
Total events	5		8			

Heterogeneity: Tau² = 1.12; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%

Test for overall effect: Z = 0.50 (P = 0.61)



3.4 First-line maintenance treatment

2b: Is sustained-release morphine more effective than sustained-release oxycodone or transdermal patches (fentanyl/buprenorphine) as first-line maintenance treatment for pain in patients with advanced and progressive disease who require strong opioids?

Evidence table 3

Citation: Bekkering, G. E., Soares-Weiser, K., Reid, K., Kessels, A. G., Dahan, A., Treede, R. D., and Kleijnen, J. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Current Medical Research and Opinion 27[7], 1477-1491. 2011.

Design: Systematic review of RCTs with network meta-analysis
Country: International
Aim: To evaluate the evidence available to support the position of morphine as the reference standard for step III opioids on efficacy and tolerability outcomes.

Inclusion criteria
RCTs that evaluated the efficacy or tolerability of step III opioids in patients aged > 18 years and suffering from cancer-related or non-cancer-related chronic pain. Studies had to compare an oral or transdermal step III opioid to placebo or to another step III opioid and report on ≥ 1 of the pre-specified outcomes of efficacy (pain intensity (PI), pain relief (PR), Patient Global Impression of Change (PGIC), quality of sleep (QoS), quality of life (QoL)) or tolerability (treatment discontinuations (TD), severe adverse events (SAE)) after ≥ 24 hours of treatment.

Exclusion criteria
Studies with a cross-over design, with N = 1, on breakthrough pain, on acute flare-ups of chronic pain, on intravenous opioids and on tapendatol.

Population
Morphine v transdermal fentanyl: 5 RCTs
- Allan et al. (2005): Low back pain; age range 21-90 years, 61% females; Fentanyl (57 µg/h) N = 338, morphine (140 mg/day) N = 342, study duration of 12-24 months; outcomes were PR, QoL, TD, SAE
- Mercadante et al. (2008): Cancer pain; age range 18-78 years, 48.6% females; Fentanyl (1.18 mg/day) N = 36, morphine (82.7 mg/day) N = 36, study duration of 7 days-1 month; outcomes were PI, QoL, TD
- Öztürk et al. (2008) [did not provide data that could be used in the meta-analysis]: Cancer pain; mean age 55 years, NR females; Fentanyl (25-100 µg/h) N = 25, morphine (20, 60, 120, 200 µg/day) N = 25, study duration of 7 days-1 month; outcome was PI
- Van Seventer et al. (2003) [patients with mild-moderate pain]: Cancer pain; age range 21-91 years, 35.1% females; Fentanyl (67 µg/h) N = 67, morphine (105 mg/day) N = 64, study duration of 7 days-1 month; outcomes were PI, PR, PGIC, QoS, TD, SAE
- Wong et al. (1997): Cancer pain; age range 30-79 years, 27.5% females; Fentanyl (61.3 µg/h) N = 20, morphine (174 mg/day) N = 20, study duration of 7 days-1 month; outcomes were PI, QoS, QoL
Morphine v oxycodone: 4 RCTs
- Mucci-LoRusso et al. (1998): Cancer pain; age range 30-83 years, 45% females; Oxycodone (101 mg/day) N = 48, morphine (140 mg/day) N = 52, study duration of 7 days-1 month; outcomes were PI, PGIC, TD
- Mercadante et al. (2010): Cancer pain; mean age range 63.2 years, 59% females; Oxycodone (20 mg/day, increased as needed) N = 30, morphine (30 mg/day, increased as needed) N = 30, study duration of 1-2 months; outcomes were PI, TD
- Nicholson et al. (2006) [patients with moderate-severe non-malignant pain]: Non-cancer pain; age range 20-83 years, 50.5% females; Oxycodone (34-84.7mg/day) N = 54, morphine (30-78.7 mg/day) N = 43, study duration of 6-11 months; outcomes were PI, PGIC, QoS, QoL, TD, SAE
- Rauck et al. (2006): Moderate-severe chronic low back pain; age range 28-73 years, 61% females; Oxycodone (53.3 mg/day) N = 189, morphine (63.7 mg/day) N = 203, study duration of 1-2 months; outcomes were PI, PR, QoL, TD, SAE
Morphine v transdermal buprenorphine: 1 RCT
- Pace et al. (2007): Cancer pain; mean age 54.5 years, 48.1% females; Buprenorphine (35-52.5 µg/h) N = 26, morphine (60-90 mg/day) N = 26, study duration of 1-2 months; outcomes were PI, PGIC, QoL, QoS.

Interventions
Sustained-release morphine v sustained-release oxycodone
Sustained-release morphine v transdermal fentanyl
Sustained-release morphine v transdermal buprenorphine

Outcomes
Pain intensity, treatment discontinuation

Results
Significant between-study heterogeneity precluded pair-wise meta-analyses. The results reported below are a result of network meta-analyses.
Effectiveness (pain intensity):
Sustained-release morphine v sustained-release oxycodone:
- Treatment duration 1 day – 1 week: Weighted mean difference (WMD) = 3.3 (95% CI -1.2 – 7.8), non-significant.
- Treatment duration 1 week – 1 month: WMD = 3.4 (95% CI -0.4 – 7.2), non-significant.
- Treatment duration > 1 month: WMD = 3.9 (95% CI -1.4 – 9.2), non-significant.
- Studies on cancer pain: WMD = 2.3 (95% CI -5.4 – 10.1), non-significant.
- Studies on non-cancer pain: **WMD = 4.6 (95% CI 0.1 – 9.1), significant. That is, in patients with non-cancer pain sustained-release morphine was significantly more effective than sustained-release oxycodone.**
Sustained-release morphine v transdermal fentanyl:
- Treatment duration 1 day – 1 week: WMD = 5.8 (95% CI -0.7 – 12.4), non-significant.
- Treatment duration 1 week – 1 month: **WMD = 8.8 (95% CI 4.2 – 13.4), significant.**
- Treatment duration > 1 month: WMD = 1 (95% CI -32.6 – 34.6), non-significant.
- Studies on cancer pain: **WMD = 8.7 (95% CI 2.7 – 14.7), significant. That is, in patients with cancer pain sustained-release morphine was significantly more effective than transdermal fentanyl.**
- Studies on non-cancer pain: WMD = 6.7 (95% CI -0.1 – 13.6), non-significant
Sustained-release morphine v transdermal buprenorphine:
- Treatment duration 1 day – 1 week: -
- Treatment duration 1 week – 1 month: **WMD = 9.6 (95% CI 3.6 – 15.6), significant. That is, in patients with treatment duration of 1 week to 1 month sustained-release morphine was significantly more effective than transdermal buprenorphine.**
- Treatment duration > 1 month: **WMD = -16.4 (95% CI -30.3 – 2.5), significant. That is, in patients with treatment duration of > 1 month transdermal buprenorphine was significantly more effective than sustained-release morphine.**
- Studies on cancer pain: **WMD = -16.4 (95% CI -29 – 3.8), significant. That is, in patients with cancer pain transdermal buprenorphine was significantly more effective than sustained-release morphine.**
- Studies on non-cancer pain: -

Treatment discontinuation (due to any reason): Studies on cancer pain
- Sustained-release morphine v sustained-release oxycodone: Odds ratio (OR) = 0.86 (95% CI 0.32 – 2.3), non-significant.
- Sustained-release morphine v transdermal fentanyl: **OR = 0.43 (95% CI 0.24 – 0.75), significant. That is, the odds of treatment discontinuation due to any reason were reduced in patients receiving transdermal fentanyl compared to patients receiving sustained-release morphine.**
- Sustained-release morphine v transdermal buprenorphine: **OR = 0.11 (95% CI 0.03 – 0.46), significant. That is, the odds of treatment discontinuation due to any reason were reduced in patients receiving transdermal buprenorphine compared to patients receiving sustained-release morphine.**
Treatment discontinuation (due to lack of efficacy): Studies on cancer pain
- Sustained-release morphine v sustained-release oxycodone: OR = 1.09 (95% CI 0.07 – 17.8), non-significant.
- Sustained-release morphine v transdermal fentanyl: OR = 1.2 (95% CI 0.39 – 3.65), non-significant.
- Sustained-release morphine v transdermal buprenorphine: OR = 0.48 (95% CI 0.07 – 3.14), non-significant.
Treatment discontinuation (due to adverse events): Studies on cancer pain
- Sustained-release morphine v sustained-release oxycodone: OR = 0.51 (95% CI 0.12 – 2.17), non-significant.
- Sustained-release morphine v transdermal fentanyl: **OR = 0.12 (95% CI 0.04 – 0.36), significant. That is, the odds of treatment discontinuation due to adverse events were reduced in patients receiving transdermal fentanyl compared to patients receiving sustained-release morphine.**
- Sustained-release morphine v transdermal buprenorphine: -

Öztürk et al. (2008):
- Pain intensity: Transdermal fentanyl = sustained-release morphine.
- **Constipation: Transdermal fentanyl (27%/N = 6) < sustained-release morphine (64%/N = 14), p = 0.03.**
- Nausea/vomiting, urinary retention, and urticaria: Transdermal fentanyl = sustained-release morphine.
- No patients developed hypoventilation

General comments
Comprehensive search of 10 databases (conducted in December 2010)
Explicit search strategy

Data extraction performed by 1 reviewer and checked by 2nd reviewer
Each study quality appraised using the Cochrane Collaboration checklist by 2 reviewers independently
Independent screening of database by 2 reviewers
Some studies not on population of interest

References of Included Studies (For systematic reviews):

- Allan, L., Richarz, U., Simpson, K., et al. Transdermal fentanyl versus sustained-release oral morphine in strong-opioid naive patients with chronic low back pain. Spine 30, 2484-90. 2005.
- Mercadante, S., Porzio, G., Ferrera, P., Fulfaro, F., Alelli, F., Verna, L., Villari, P., Ficorella, C., Gebbia, V., Riina, S., Casuccio, A., and Mangione, S. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. European Journal of Pain 12[8], 1040-1046. 2008.
- Mercadante, S., Tirelli, W., David, F., Arcara, C., Fulfaro, F., Casuccio, A., Gebbia, V., Mercadante, Sebastiano, Tirelli, Walter, David, Fabrizio, Arcara, Carlo, Fulfaro, Fabio, Casuccio, Alessandra, and Gebbia, Vittorio. Morphine versus oxycodone in pancreatic cancer pain: a randomized controlled study. Clinical Journal of Pain 26[9], 794-797. 2010.
- Mucci-LoRusso, P., Berman, B. S., Silberstein, P. T., Citron, M. L., Bressler, L., Weinstein, S. M., Kaiko, R. F., Buckley, B. J., Reder, R. F., Mucci-LoRusso, P., Berman, B. S., Silberstein, P. T., Citron, M. L., Bressler, L., Weinstein, S. M., Kaiko, R. F., Buckley, B. J., and Reder, R. F. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain: a randomized, double-blind, parallel-group study. European Journal of Pain: Ejp 2[3], 239-249. 1998.
- Nicholson, B., Ross, E., Sasaki, J., Weil, A., Nicholson, Bruce, Ross, Edgar, Sasaki, John, and Weil, Arnold. Randomized trial comparing polymer-coated extended-release morphine sulfate to controlled-release oxycodone HCl in moderate to severe non-malignant pain. Current Medical Research & Opinion 22[8], 1503-1514. 2006.
- Öztürk, T., Karadibak, K., Catal, D., et al. [Comparison of TD-fentanyl with sustained-release morphine in the pain treatment of patients with lung cancer]. Agri 20, 20-5. 2008.
- Pace, M. C., Passavanti, M. B., Grella, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., Aurilio, C., Pace, Maria Caterina, Passavanti, Maria Beatrice, Grella, Elisa, Mazzariello, Luigi, Maisto, Massimo, Barbarisi, Manlio, Baccari, Ena, Sansone, Pasquale, and Aurilio, Caterina. Buprenorphine in long-term control of chronic pain in cancer patients. Frontiers in Bioscience 12, 1291-1299. 2007.
- Rauck, R.L., Bookbinder, S.A., Bunker, T.R., et al. The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulphate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. J Opioid Manag 3, 155-6. 2006.
-van, Seventer R., Smit, J. M., Schipper, R. M., Wicks, M. A., and Zuurmond, W. W. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. SO: Current medical research and opinion 19[6], 457-469. 2003.
- Wong J.O., Chiu, G.L., Tsao, C.J., et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. Acta Anaesthesiol Sinica 35, 25-32. 1997.

Citation: Caraceni, A., Pigni, A., Brunelli, C., Caraceni, Augusto, Pigni, Alessandra, and Brunelli, Cinzia. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. Palliative Medicine 25[5], 402-409. 2011.

Design: Systematic review w/o/ meta-analysis
Country: Italy
Aim: To evaluate the evidence that oral morphine can be recommended as the first choice opioid in the treatment of moderate to severe cancer pain.

Inclusion criteria
RCTs, or meta-analyses of reported data, conducted in human, 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 (e.g., methadone, oxycodone, hydromorphone, fentanyl, and buprenorphine also in the transdermal mode of administration) written in English.

Exclusion criteria
Studies dealing with the use of morphine for breakthrough pain management were excluded.

Population
See **Results** section.

Interventions
Modified-release morphine v transdermal fentanyl
Modified-release morphine v modified-release oxycodone

Outcomes
Efficacy, side effects.

Results The authors aimed to do a meta-analysis, but did not find that the data were compatible with this aim. The results of the relevant (for the present purposes) included studies reporting data not elsewhere included in this evidence review are therefore reported narratively:
- Ahmedzai et al. (1997): Comparator: Modified-release morphine v transdermal fentanyl (cross-over trial). N = 202, previous opioid treatment (WHO ladder) = III. Study limitations: No allocation concealment, large losses to follow up. Drop-out rate = 45%. Reported efficacy: Not evidence of difference. Side effects: See evidence table for Tassanari et al. (2008).
- Lauretti et al. (2003): Comparator: Modified-release morphine v modified-release oxycodone (double-blind cross-over trial). N = 26, previous opioid treatment (WHO ladder) = II (tramadol). Study limitations: None listed. Drop-out rate = 15%. Reported efficacy: Not evidence of difference. Side effects: Morphine > nausea & vomiting.

General comments
Comprehensive explicit search strategy
Separately screening and assessment for inclusion by 2 review authors

References of Included Studies (For systematic reviews):
- Ahmedzai, S., Brooks, D., on behalf of the TTS-Fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy and quality of life. J Pain Symptom Manage 13, 254-61. 1997.
- Lauretti, G.R., Oliveira, G.M. and Pereira, N.L. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. Br J Cancer 89: 2027–2030. 2003.

Citation: Reid, C. M., Martin, R. M., Sterne, J. A. C., Davies, A. N., and Hanks, G. W. Oxycodone for cancer-related pain - Meta-analysis of randomized controlled trials. Archives of Internal Medicine 166[8], 837-843. 2006.

Design: Systematic review w/ meta-analysis
Country: United Kingdom
Aim: To evaluate the efficacy and tolerability of oxycodone in cancer-related pain,

Inclusion criteria
RCTs comparing oxycodone with placebo or an active analgesic drug in patients with cancer-related pain. All routes of drug administration and all formulations of oxycodone were considered.

Exclusion criteria
Studies of combination oxycodone preparations (eg, oxycodone and acetaminophen).

Population
6 RCTs, 2 of which were not included in the meta-analysis (which is not a problem for the present purposes as 1 of them, Kalso & Vainio (1990), used immediate-release preparations and the other (Beaver et al., 1978) compared intramuscular preparations.
The remaining 4 RCTs (all lasting from 10-20 days) were:
- Bruera et al. (1998): Double-blind cross-over study of patients with stable cancer pain (≥ 3 d of stable opioid doses). Number of patients entered/completed and withdrawals: 32/23, 9 Withdrawals of which 5 were due to adverse events (3 with morphine; 2 with oxycodone) and 4 for other reasons. Intervention: 7 d of each drug (crossover day 8), dose adjustments permitted until pain control achieved, rescue dose, 10% of 24-h dose, dose titration similar in both groups, mean morphine dosage = 72.6 mg every 12 h; mean oxycodone dosage = 46.5 mg every 12 h. Median morphine-oxycodone ratio = 1.5. Outcomes reported: Pain measured on VAS (10 cm) and CAT (0-4), no significant difference in pain intensity scores between treatments, no statistically significant differences in mean severity of any adverse events or in patient preference. Notes: Funded by pharmaceutical company.
- Hagen & Babul (1997): *Controlled-release hydromorphone v controlled-release oxycodone:* Double-blind crossover study of patients with chronic stable cancer pain (≥ 3 d of stable opioid doses; mean age = 56 years). Number of patients entered/completed and withdrawals: 44/31, 13 Withdrawals, of which 8 were due to adverse events (6 with oxycodone; 2 with hydromorphone) and 5 for other reasons. Interventions: 7 d of each drug (crossover day 8), dose adjustments permitted until pain control achieved, rescue dose = 10% of 24-h dose, dose titration similar in both groups, mean hydromorphone dosage = 30 mg per 24 h; mean oxycodone dosage = 124 mg per 24 h, hydromorphone-oxycodone ratio = 1.6. Outcomes reported: Pain measured on VAS (10 cm) and 5-point CAT (0-4), overall mean pain intensity across all days: VAS = 28 mm (CR oxycodone) and 31 mm (CR hydromorphone) (p = .1), CAT = 1.4 (CR oxycodone) and 1.5 (CR hydromorphone) (p = .10), nausea and sedation measured on 10-cm VAS, no significant differences in nausea or sedation scores or patient preference between groups. Notes: Funded by pharmaceutical company.

- Heiskanen & Kalso (1997): Double-blind cross-over study of patients with chronic stable cancer pain (mean age = 60 years). Number of patients entered/completed and withdrawals: 45/27, 18 withdrawals, of which 7 were due to adverse events (5 with oxycodone; 2 with morphine) and 11 for other reasons. Intervention: Initial open-label dose titration phase until 48 h of effective pain relief, followed by crossover sequences lasting 3-6 d, rescue dosage, 1⁄6 to 1⁄8 of 24-h dose, dose titration similar in both groups, mean morphine dosage = 180 mg in 24 h, mean oxycodone dosage = 123 mg in 24 h, morphine-oxycodone ratio = 1.5. Outcomes reported: Pain measured on 4-point verbal rating scale, when stable phases were combined, pain control was better with CR morphine than with CR oxycodone, constipation was more common with oxycodone, vomiting with morphine, night time acceptability was better in morphine group. Notes: Assistance from Pharmaceutical company.
- Mucci-LaRusso et al. (1998): Double-blind parallel group of patients with chronic cancer pain requiring 30 to 340 mg of oxycodone or equivalent (mean age = 59 years). Number of patients entered/completed and withdrawals: 101/79, 21 withdrawals, of which 9 were due to adverse events (3 with oxycodone and 6 with morphine), 12 for other reasons (1 patient did not receive any medication). Intervention: Initial doses of study medication calculated from prestudy opioid requirements, dose titrated up until stable pain control for 48 h Dose titration similar in both groups, mean morphine dosage = 140 mg in 24 h, mean oxycodone dosage = 101 mg in 24 h, rescue dose = 1/6-1/8 of 24-h dose, morphine-oxycodone ratio = 1.4. Outcomes reported: Pain on 4-point CAT (0-3), pain scores from last 48 h of study used in efficacy analyses, reduction in mean pain scores of 0.6 from baseline in both groups, no statistically significant difference between treatments noted, no difference in quality of life scores or patient preference between groups. Notes: Funded by pharmaceutical company.

Interventions

Controlled-release morphine v controlled-release oxycodone
Controlled-release hydromorphone v controlled-release oxycodone

Outcomes

Pain intensity, adverse events

Results

Pain intensity: Controlled-release morphine v controlled-release oxycodone (meta-analysis):
Standardised weighted mean differences (WMD) = 0.20 (95% CIO -0.04 – 0.44, non-significant; I^2 = 0%)
See also the **Population** section above for information on the results of the individual studies.

Adverse events: Controlled-release morphine/hydromorphone v controlled-release oxycodone (meta-analysis):
- Nausea: Odds ratio (OR) = 0.75 (95% CI 0.51-1.1), non-significant, I^2 = 0%. Percentage of study completers experiencing nausea on oxycodone = 53% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), 42% (Mucci-LoRusso et al., 1998) and 64% (Hagen & Babul, 1997), and percentage of study completers experiencing nausea on morphine = 53% (Heiskanen & Kalso, 1997), 74% (Bruera et al., 1998), and 48% (Mucci-LoRusso et al., 1998) and on hydromorphone 68% (Hagen & Babul, 1997).
- Constipation: OR = 1.22 (95% CI 0.76-1.95), non-significant, I^2 = 39%. Percentage of study completers experiencing constipation on oxycodone = 53% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), 35% (Mucci-LoRusso et al., 1998) and 74% (Hagen & Babul, 1997), and percentage of study completers experiencing constipation on morphine = 49% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), and 21% (Mucci-LoRusso et al., 1998) and on hydromorphone 61% (Hagen & Babul, 1997).
- Drowsiness (excluding hydromorphone trial): OR = 0.72 (95% CI 0.47-1.1), non-significant, I^2 = NR. Percentage of study completers experiencing drowsiness on oxycodone = 49% (Heiskanen & Kalso, 1997), 87% (Bruera et al., 1998), and 31% (Mucci-LoRusso et al., 1998), and percentage of study completers experiencing drowsiness on morphine = 57% (Heiskanen & Kalso, 1997), 87% (Bruera et al., 1998), and 31% (Mucci-LoRusso et al., 1998).
- Difficulty concentrating: OR = 0.93 (95% CI 0.72-1.21), non-significant, I^2 = 0%. Percentage of study completers experiencing difficulty concentrating on oxycodone = 4% (Heiskanen & Kalso, 1997), 52% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 58% (Hagen & Babul, 1997), and percentage of study completers experiencing difficulty concentrating on morphine = 4% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).
- Hallucinations: OR = 1.46 (95% CI 0.69-3.07), non-significant, I^2 = 0%. Percentage of study completers experiencing hallucinations on oxycodone = 0% (Heiskanen & Kalso, 1997), 30% (Bruera et al., 1998), 0% (Mucci-LoRusso et al., 1998) and 0% (Hagen & Babul, 1997), and percentage of study completers experiencing hallucinations on morphine = 0% (Heiskanen & Kalso, 1997), 17% (Bruera et al., 1998), and 4% (Mucci-LoRusso et al., 1998) and on hydromorphone 6% (Hagen & Babul, 1997).
- Dry mouth (excluding hydromorphone trial): **OR = 0.56 (95% CI 0.38-0.83), significant, but I^2 = NR**. Percentage of study completers experiencing dry mouth on oxycodone = 35% (Heiskanen & Kalso, 1997), 74% (Bruera et al., 1998), and 33% (Mucci-LoRusso et al., 1998), and percentage of study completers experiencing dry mouth on morphine = 47% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), and 48% (Mucci-LoRusso et al., 1998).
- Vomiting: OR = 0.72 (95% CI 0.49-1.06), non-significant, I^2 = 0%. Percentage of study completers experiencing vomiting on oxycodone = 31% (Heiskanen & Kalso, 1997), 9% (Bruera et al., 1998), 0% (Mucci-LoRusso et al., 1998) and 26% (Hagen & Babul, 1997), and percentage of study completers experiencing vomiting on morphine = 35% (Heiskanen & Kalso, 1997), 22% (Bruera et al., 1998), and 2% (Mucci-LoRusso et al., 1998) and on hydromorphone 29% (Hagen & Babul, 1997).
- Agitation: OR = 1.12 (95% CI 0.78-1.61), non-significant, I^2 = 0%. Percentage of study completers experiencing agitation on oxycodone = 0% (Heiskanen & Kalso, 1997), 70% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 32% (Hagen & Babul, 1997), and percentage of study completers experiencing agitation on morphine = 2% (Heiskanen & Kalso, 1997), 52% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 32% (Hagen & Babul, 1997).

- Dizziness: OR = 0.89 (95% CI 0.48-1.66), non-significant, I^2 = 63%. Percentage of study completers experiencing dizziness on oxycodone = 20% (Heiskanen & Kalso, 1997), 39% (Bruera et al., 1998), 21% (Mucci-LoRusso et al., 1998) and 35% (Hagen & Babul, 1997), and percentage of study completers experiencing dizziness on morphine = 24% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and 31% (Mucci-LoRusso et al., 1998) and on hydromorphone 26% (Hagen & Babul, 1997).
- Poor sleep: OR = 0.79 (95% CI 0.42-1.48), non-significant, I^2 = 27%. Percentage of study completers experiencing poor sleep on oxycodone = 0% (Heiskanen & Kalso, 1997), 65% (Bruera et al., 1998), 2% (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing poor sleep on morphine = 0% (Heiskanen & Kalso, 1997), 56% (Bruera et al., 1998), and 2% (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).
- Twitching: OR not estimable because no individuals had discordant adverse effects. Percentage of study completers experiencing twitching on oxycodone = 2% (Heiskanen & Kalso, 1997), 48% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 29% (Hagen & Babul, 1997), and percentage of study completers experiencing twitching on morphine = 2% (Heiskanen & Kalso, 1997), 35% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 29% (Hagen & Babul, 1997).
- Fatigue: OR = 0.92 (95% CI 0.54-1.58), non-significant, I^2 = 0%. Percentage of study completers experiencing fatigue on oxycodone = 2% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 77% (Hagen & Babul, 1997), and percentage of study completers experiencing fatigue on morphine = 0% (Heiskanen & Kalso, 1997), 83% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).
- Itch: OR = 1.12 (95% CI 0.8-1.56), non-significant, I^2 = 0%. Percentage of study completers experiencing itch on oxycodone = 22% (Heiskanen & Kalso, 1997), 35% (Bruera et al., 1998), 20% (Mucci-LoRusso et al., 1998) and 55% (Hagen & Babul, 1997), and percentage of study completers experiencing itch on morphine = 24% (Heiskanen & Kalso, 1997), 43% (Bruera et al., 1998), and 21% (Mucci-LoRusso et al., 1998) and on hydromorphone 45% (Hagen & Babul, 1997).
- Vivid dreams: OR = 1.21 (95% CI 0.65-2.27), non-significant, I^2 = 0%. Percentage of study completers experiencing vivid dreams on oxycodone = 2% (Heiskanen & Kalso, 1997), 26% (Bruera et al., 1998), NR (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing vivid dreams on morphine = 0% (Heiskanen & Kalso, 1997), 22% (Bruera et al., 1998), and NR (Mucci-LoRusso et al., 1998) and on hydromorphone 32% (Hagen & Babul, 1997).
- Headache: OR = 0.93 (95% CI 0.51-1.68), non-significant, I^2 = 22%. Percentage of study completers experiencing headache on oxycodone = 4% (Heiskanen & Kalso, 1997), 43% (Bruera et al., 1998), 10% (Mucci-LoRusso et al., 1998) and 39% (Hagen & Babul, 1997), and percentage of study completers experiencing headache on morphine = 4% (Heiskanen & Kalso, 1997), 30% (Bruera et al., 1998), and 6% (Mucci-LoRusso et al., 1998) and on hydromorphone 55% (Hagen & Babul, 1997).
- Sweating: OR = 1.05 (95% CI 0.71-1.56), non-significant, I^2 = 0%. Percentage of study completers experiencing sweating on oxycodone = 35% (Heiskanen & Kalso, 1997), 61% (Bruera et al., 1998), 4% (Mucci-LoRusso et al., 1998) and 55% (Hagen & Babul, 1997), and percentage of study completers experiencing sweating on morphine = 31% (Heiskanen & Kalso, 1997), 48% (Bruera et al., 1998), and 4% (Mucci-LoRusso et al., 1998) and on hydromorphone 61% (Hagen & Babul, 1997).

General comments

Comprehensive search conducted
The full-text versions of potentially eligible articles independently assessed by 2 of the investigators
Independent data extraction from included trials by 2 authors
Quality of included studies not high
Vast majority of adverse events analyses includes hydromorphone trial
Not first-line in all patients

References of Included Studies (For systematic reviews):

- Beaver WT,Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer, II: comparisons of intramuscular oxycodone with intramuscular morphine and codeine. J Pharmacol Exp Ther. 978;207:101-
108.
- Bruera E, Belzile M, Pituskin E, et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol. 1998;16: 3222-3229.
- Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. Cancer. 1997;79:1428-1437.
- Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain. 1997;73:37-45.
- Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther*. 1990;47:639-646.
- Mucci-LoRusso P, Berman B, Silberstein P, et al. Controlled-release oxycodone compared with controlled-release morphine in the treatment of cancer pain. Eur J Pain. 1998;2:239-249.

Citation: Tassinari, D., Sartori, S., Tamburini, E., Scarpi, E, Raffaeli, W., Tombesi, P., & Maltoni, M. (2008). Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: A meta-analysis and systematic review of the literature. Journal of Palliative Medicine, 11, 492-501.

Design: Systematic review w/ meta-analysis
Country: Italy

Aim: To assess the adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison with slow release oral morphine.

Inclusion criteria
Phase 3 RCTs comparing slow-release morphine to transdermal opiates in patients with moderate-severe cancer pain with a defined need for opiates at the time of entering the trial

Exclusion criteria
Randomised phase 2 trials, trials comparing the outcomes with a historical arm or literature data, trials with patients with non-cancer pain, trials not reporting safety data or not reporting adequate information about randomisation process in methods/results section, trials including patients treated with analgesic approaches other than morphine or transdermal opiates, and trials including patients needing an opiate titration at the time of entering the trial.

Population
4 RCTs:
Transdermal fentanyl v slow-release morphine:
- Ahmedzai et al. (1997): N = 202; randomised cross-over trial using 'oral morphine 1 mg/transdermal fentanyl 10 µg' ratio as equianalgesic doses of patients; Jadad score = 3 (moderate quality).
- van Seventer et al. (2003): N = 131; fentanyl daily dose = 600 µg v morphine daily dose = 60 mg; Jadad score = 3 (moderate quality).
- Wong et al. (1997): N = 47; fentanyl daily dose = 1260 ± 183 µg v morphine daily dose = 137 ± 18.3 mg; Jadad score = 2 (low quality).
Transdermal buprenorphine v slow-release morphine:
- Pace et al. (2007): N = 52; buprenorphine daily dose = 840 µg v morphine daily dose = 60 mg; Jadad score = 2 (low quality).

Interventions
Transdermal fentanyl v slow-release morphine
Transdermal buprenorphine v slow-release morphine

Outcomes
Overall adverse effects, overall neurological (insomnia, drowsiness, confusion, headache and vertigo) and gastrointestinal (constipation, diarrhea, anorexia, nausea, vomiting and itching) adverse effects, constipation, nausea, drowsiness, patients' preference and trial withdrawal.

Results Meta-analyses were performed based on the data extracted by Tassinari et al. (2008), but subgrouped by type of transdermal opioid, which constituted analyses not reported by Tassinari et al. (2008).

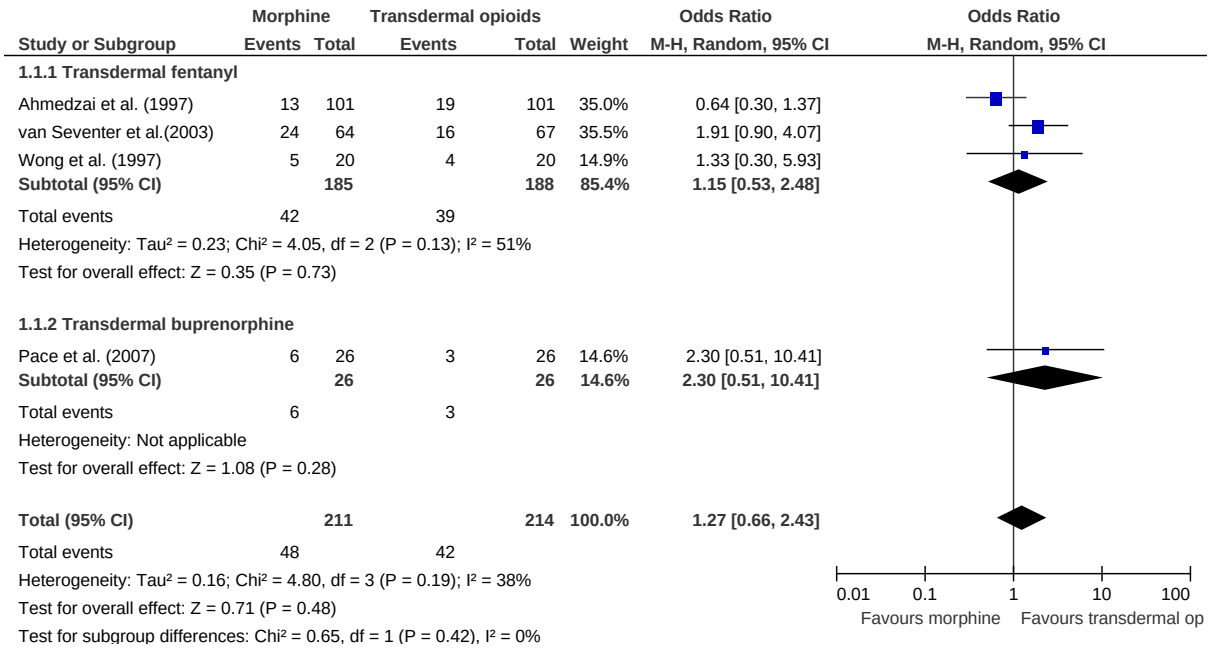
The table below lists the results of the analyses (see also the forest plots below for more detail). From the table and the forest plots it is evident that the treatments did not differ significantly in terms of any of the side effects apart from the following where the transdermal option was favoured in each case: Overall gastrointestinal side effects (buprenorphine treatment only), constipation (fentanyl and buprenorphine) and patient preference (fentanyl only).

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Overall side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.66, 2.43]
1.1.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.53, 2.48]
1.1.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	2.30 [0.51, 10.41]
1.2 Overall gastrointestinal side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.66, 3.08]
1.2.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.56, 2.05]
1.2.2 Transdermal buprenorphine	**1**	**52**	**Odds Ratio (M-H, Random, 95% CI)**	**4.79 [1.14, 20.21]**
1.3 Nausea	4	425	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.57, 2.36]
1.3.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]

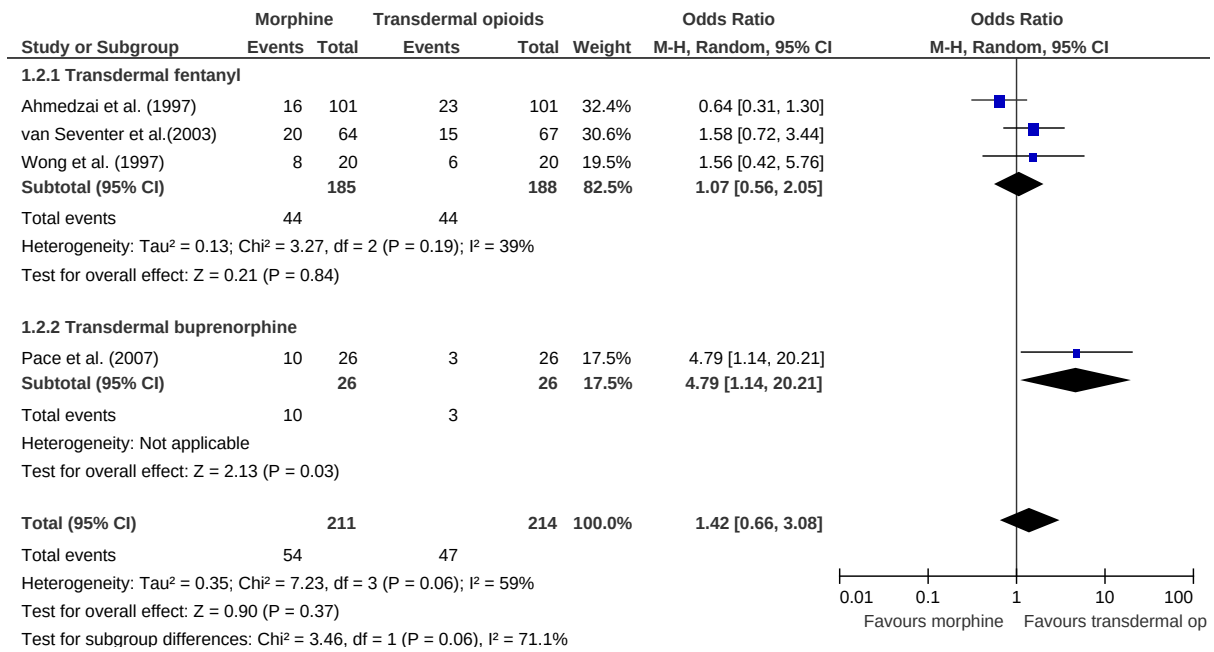
1.3.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	4.06 [0.95, 17.29]
1.4 Constipation	4	425	Odds Ratio (M-H, Random, 95% CI)	2.63 [1.57, 4.39]
1.4.1 Transdermal fentanyl	**3**	**373**	**Odds Ratio (M-H, Random, 95% CI)**	**2.35 [1.37, 4.03]**
1.4.2 Transdermal buprenorphine	**1**	**52**	**Odds Ratio (M-H, Random, 95% CI)**	**7.50 [1.45, 38.85]**
1.5 Overall neurological side effects	4	425	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.95, 3.10]
1.5.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.78, 3.57]
1.5.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.39, 8.59]
1.6 Drowsiness	4	425	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.81, 3.06]
1.6.1 Transdermal fentanyl	3	373	Odds Ratio (M-H, Random, 95% CI)	1.75 [0.85, 3.59]
1.6.2 Transdermal buprenorphine	1	52	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.10, 4.18]
1.7 Patient preference	3	373	Odds Ratio (M-H, Random, 95% CI)	2.32 [1.19, 4.54]
1.7.1 Transdermal fentanyl	**3**	**373**	**Odds Ratio (M-H, Random, 95% CI)**	**2.32 [1.19, 4.54]**
1.8 Hypoventilation	2	242	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.30]
1.8.1 Transdermal fentanyl	2	242	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.30]

Trial withdrawal and changes in opiate treatment was reported in 2 trials (not reported which 2 trials) and heterogeneity was found for both of these outcomes ($p < 0.001$ and $p = 0.008$, respectively; ORs = 0.62, $p = 0.59$; and OR = 0.575, $p = 0.607$, respectively)

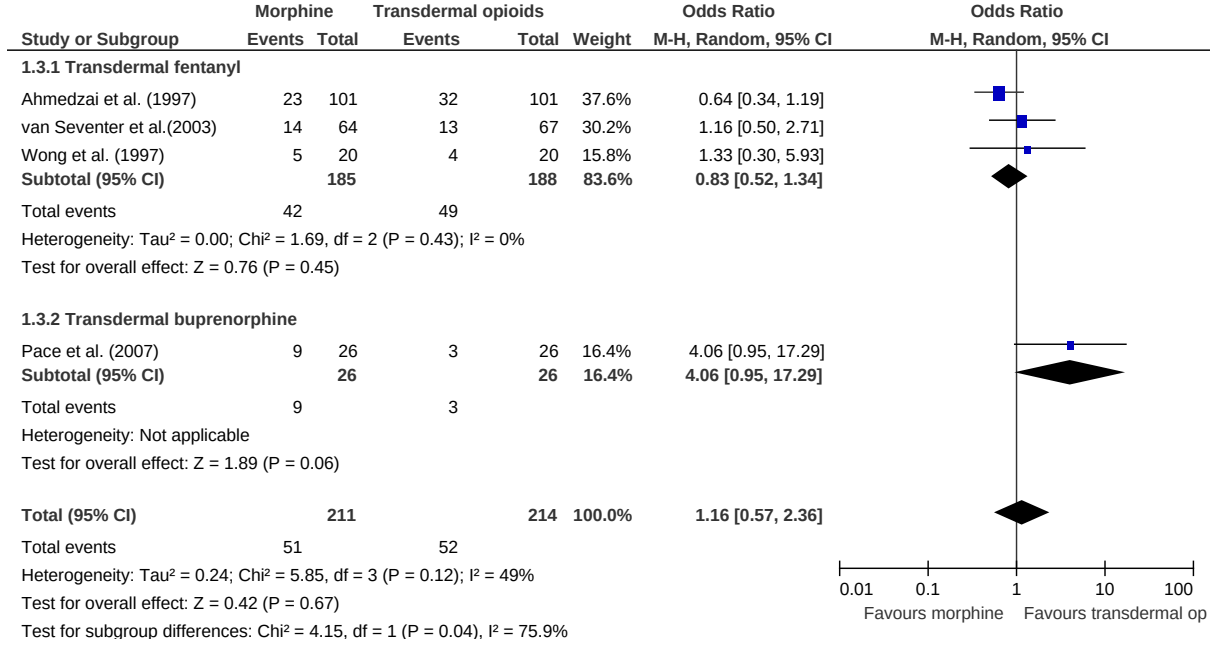
Overall side effects:



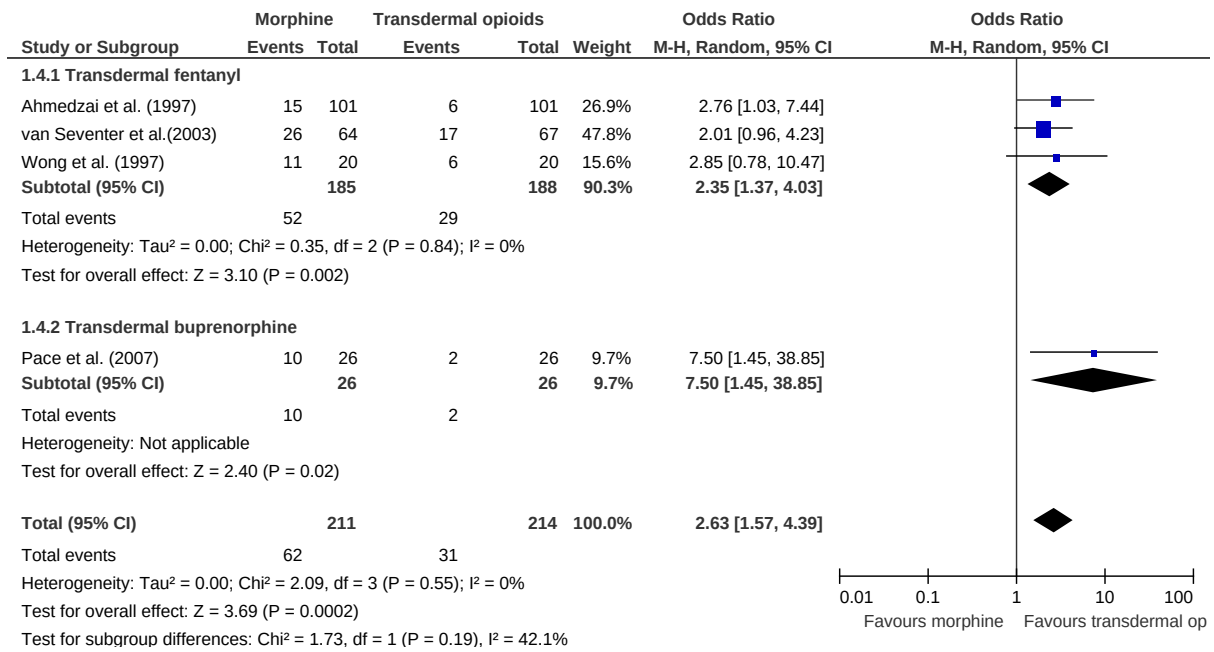
Overall gastrointestinal side effects:



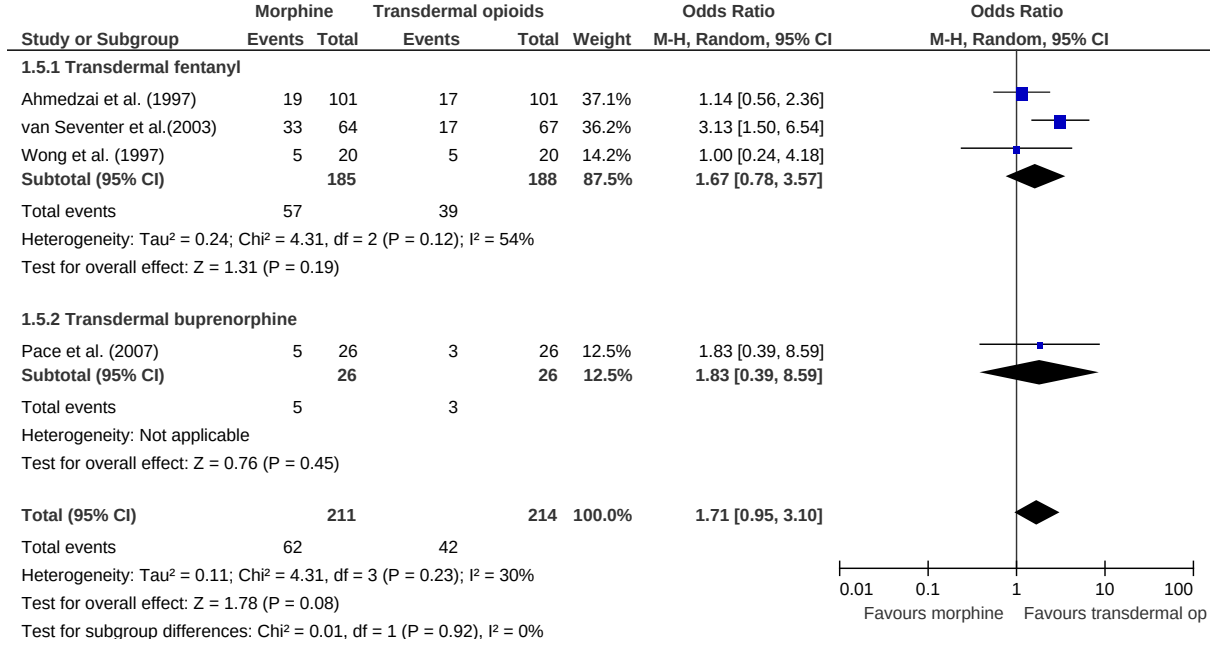
Nausea:



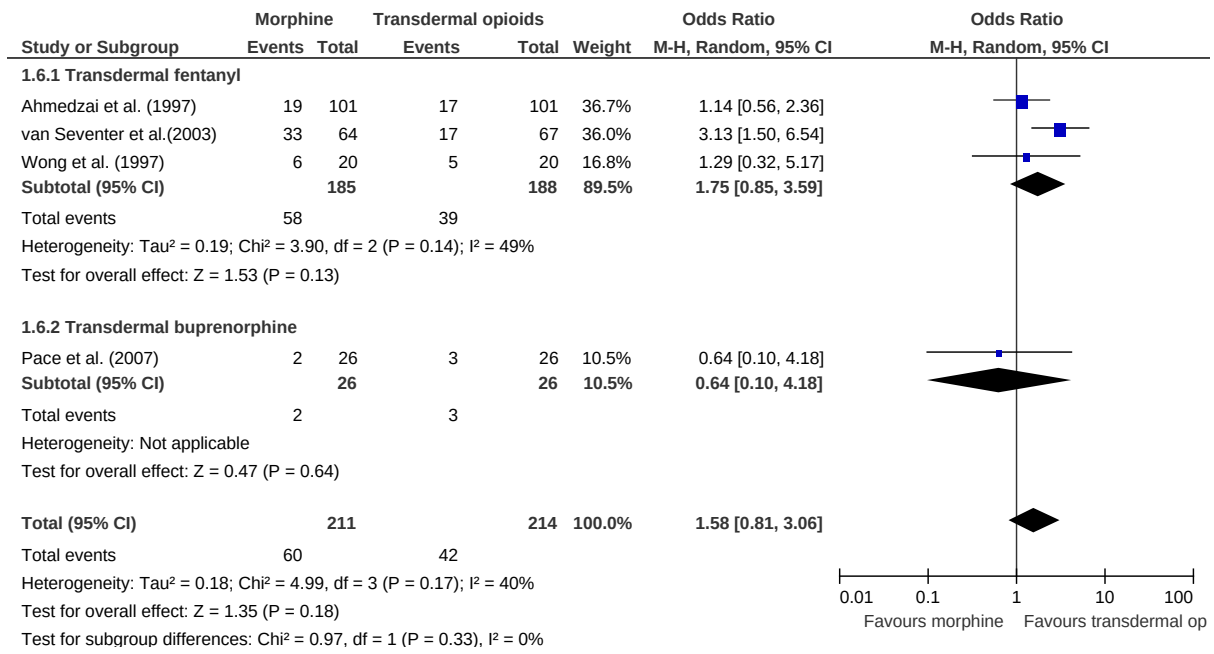
Constipation:



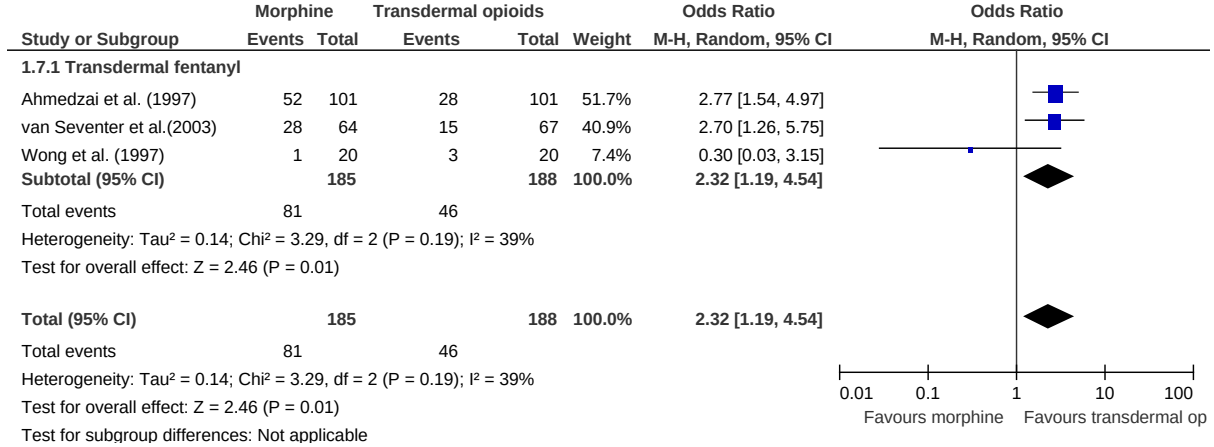
Overall neurological side effects:



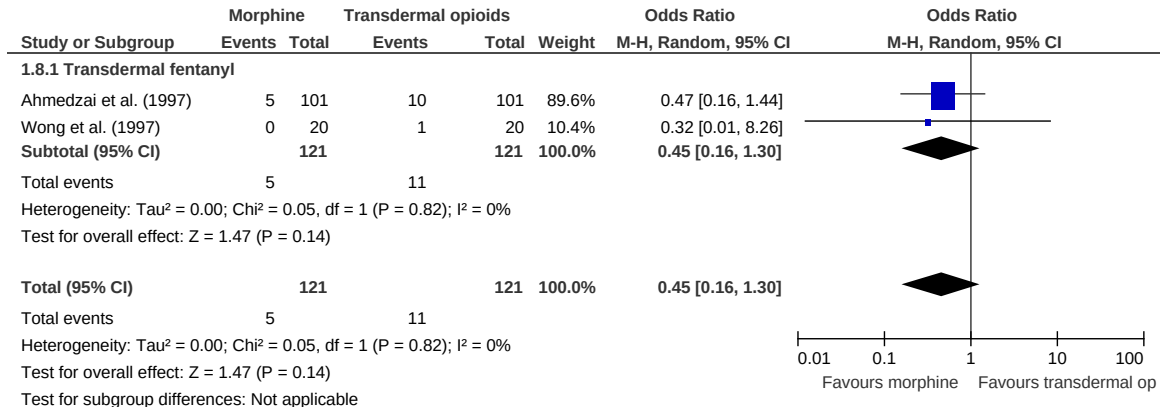
Drowsiness:



Patient preference:



Hypoventilation:



General comments

Systematic search of MEDLINE and EMBASE from 1966-2006, performed independently by 2 authors
Selected trials were independently assigned a JADAD score by 2 authors
Heterogeneity reported
Not first-line treatment in all the studies

References of Included Studies (For systematic reviews):
- Ahmedzai , S., Brooks, D., on behalf of the TTS-Fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy and quality of life. J Pain Symptom Manage 13, 254-61. 1997.
- Pace, M. C., Passavanti, M. B., Grella, E., Mazzariello, L., Maisto, M., Barbarisi, M., Baccari, E., Sansone, P., Aurilio, C., Pace, Maria Caterina, Passavanti, Maria Beatrice, Grella, Elisa, Mazzariello, Luigi, Maisto, Massimo, Barbarisi, Manlio, Baccari, Ena, Sansone, Pasquale, and Aurilio, Caterina. Buprenorphine in long-term control of chronic pain in cancer patients. Frontiers in Bioscience 12, 1291-1299. 2007.
-van, Seventer R., Smit, J. M., Schipper, R. M., Wicks, M. A., and Zuurmond, W. W. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. SO: Current medical research and opinion 19[6], 457-469. 2003.
- Wong J.O., Chiu, G.L., Tsao, C.J., et al. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. Acta Anaesthesiol Sinica 35, 25-32. 1997.

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

Design: Abstract on the pooled analysis of two open randomised parallel 4-week studies
Country: Europe
Aim: to compare the safety and efficacy of transdermal fentanyl with sustained release morphine (SRM), in the treatment of strong-opioid-naïve patients, and patients transferring from weak to strong opioids, with chronic cancer pain.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population

Not reported

Interventions
Transdermal fentanyl: Transdermal fentanyl was prescribed the lowest dose, 25 µg/h patch every 72 hours, with incremental titration of 25 µg/h to achieve adequate pain control.
Sustained-release morphine: Starting dose of 30 mg sustained-release morphine 12 hourly.

Outcomes
Constipation, pain control, drowsiness, sleep quality and overall patient satisfaction with treatment.

Results
- At day 7, significantly more patients were constipated in the sustained-release morphine group compared with the transdermal fentanyl group ($p = 0.002$).
- Pain control: Sustained-release morphine = transdermal fentanyl
- Side effects: Transdermal fentanyl < sustained-release morphine ($p=0.01$)
- Convenience of use: Transdermal fentanyl > sustained-release morphine ($p=0.01$)
- Overall impression: Transdermal fentanyl = sustained-release morphine ($p=0.06$)
- Compared to baseline, at the end of study transdermal fentanyl patients suffered significantly less ($p=0.02$) from troublesome side effects compared to patients treated with sustained-release morphine.
- More patients treated with sustained-release morphine withdrew from the study due to adverse events compared to the transdermal fentanyl group [but it is not reported whether this is numerically more or significantly more patients].

General comments
These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

References of Included Studies (For systematic reviews): NA

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

2c: Are fentanyl patches more effective than 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?

Evidence tables 4

Citation: Sarhan T, & Doghem M. A comparison of two trans-dermal drug delivery systems; Buprenorphine and fentanyl for chronic cancer pain management. European Journal of Pain Conference[var.pagings], September. 2009.
Design: RCT (parallel groups; abstract only) **Country**: Egypt **Aim**: To compare three escalating doses of transdermal fentanyl and transdermal buprenorphine for chronic cancer pain management.
Inclusion criteria None reported
Exclusion criteria None reported
Population N = 32 opioid naive patients suffering from chronic cancer pain with visual analogue scale (VAS) ≥7, randomly allocated into one of two groups with N = 16 patients each
Interventions Fentanyl: Transdermal fentanyl patches every 3 days starting with 25 µg/h escalated to 50 µg/h and then gradually to 75 µg/h patch for VAS ≤ 3 . Buprenorphine: Buprenorphine trans-dermal opioid patches starting with a doses of 35 µg/h, increased to 52.5µg/h patch and gradually to 70 µg/h for VAS ≤ 3.
Outcomes Severity of pain by VAS (every 3 days), mean number of each category patch dose, treatment satisfaction, mean daily dose of diclofenac sodium, mean cost of treatment, side effects and complications. Measured for 6 weeks.
Results No statistically significant differences in the mean VAS and other measurements before and for 6 weeks of treatment between (?) the groups. Drowsiness and local skin complication: Buprenorphine > fentanyl
General comments - Random allocation - Measurements done by an assessor blinded to the study - These data are only published in abstract form and it is therefore not possible to appraise the study. The results should therefore be treated with extreme caution.

Citation: Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, Standop J, Kloecker N, Nadstawek J. (2009). Gastrointestinal symptoms under opioid therapy: A prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. European Journal of Pain 13; 737-43.
Design: Prospective controlled trial **Country**: Germany **Aim**: To evaluate the effect of long-term treatment with oral sustained-release hydromorphone, transdermal fentanyl and transdermal buprenorphine on nausea, emesis and constipation. *Only data pertaining to the comparison between transdermal fentanyl and transdermal buprenorphine [as outlined in the PICO] will be reported.*
Inclusion criteria *Patients were randomly selected* "After identifying outpatients undergoing pain therapy consisting of one of the study medications, patients were selected for participation by a computer generated random selection scheme. In accordance with the requirements of the local ethics committee, we first selected patients by randomly and then asked them to participate after giving their informed consent.

To avoid opioid-naive patients being enrolled, only patients who had already taken one of the study medications for longer than 4 weeks were included. After the enrolment of 62 patients per group the study was finalised." Page 738

Patients with cancer related pain, pure nociceptive pain, opioid therapy with one of the study medications for longer than 28 days, strictly ambulatory treatment, the patient's cooperation, and a score of 0–3 on the ECOG Performance Status scale.

Exclusion criteria
Referral for inpatient treatment diarrhoea and diseases that are likely to cause diarrhoea (e.g. carcinoma of the pancreas), neuropathic or mixed pain, breakthrough pain, severe incidental pain (NRS > 5), communication deficits, hepatic or renal impairment with the risk of accumulation, conditions likely to interfere with transdermal or oral administration or with drug absorption, current chemotherapy, radiotherapy, immobilization or inability to walk, entering the terminal phase, infections, prior history of drug addiction or alcohol abuse, and concomitant treatment with other opioid analgesics during the study period. Modification of the dose of study opioids was a particular reason for exclusion.

Population
Fentanyl: N = 55 randomly selected patients; mean age = 64.1 (SD = 11.6) years; 28 males; mean ECOG score = 2.1 (SD = 1.3); mean EORTC item 1 = 3 (SD = 1.2); mean EORTC item 2 = 3 (SD = 1.1); mean EORTC item 3 = 2.5 (SD = 1.2); mean EORTC item 4 = 2.4 (SD = 1.4); mean EORTC item 5 = 1.6 (SD = 1); mean pain at rest = 2.8 (SD = 2.8); mean duration of opioid use = 206.9 (SD = 291.2) days; mean morphine equivalent (1:100) opioid daily dose = 183.3 (SD = 131.74) mg; use of dipyrone: N = 26; use of NSAIDS: N = 14; Patients with a constipating medication: N = 28; Amitriptyline: N = 4 (mean = 31.3 (SD = 12.5) mg/d); Verapamil: N = 0; Nifedipine: N = 0; Furosemide: N = 7 (mean = 33.3 (SD = 11.5) mg); Pantoprazole: N = 24 (mean =47.1 (SD = 21) mg); Antiemetics (except metoclopramide): N = 16; Haloperidol: N = 4 (mean = 1.9 (SD = 1.2) mg/d); Promethazine: N = 2 (mean = 17.5 (SD = 10.6) mg; Dimenhydramine: N = 1 (mean = 25 mg/d); Ondansetrone: N = 0; hypertension: N = 5; mild coronary heart disease: N = 2; pulmonary diseases: N = 4; history of cardiac arrhythmia: N = 0. Renal or hepatic impairment: N = 0. Transmucosal fentanyl: N = 5.
Buprenorphine: N = 61 randomly selected patients; mean age = 65.3 (SD = 10.7) years; 36 males; mean ECOG score = 1.9 (SD = .8); mean EORTC item 1 = 3.5 (SD = .8); mean EORTC item 2 = 3.4 (SD = .7); mean EORTC item 3 = 2.2 (SD = 1); mean EORTC item 4 = 2.2 (SD = .9); mean EORTC item 5 = 1.4 (SD = .8); mean pain at rest = 3 (SD = 2.3); mean duration of opioid use = 174.1 (SD = 222.5) days; mean morphine equivalent (1:75) opioid daily dose = 88.52 (SD = 39.8) mg; use of dipyrone: N = 23; use of NSAIDS: N = 14; Patients with a constipating medication: N = 28; Amitriptyline: N = 10 (mean = 30 (SD = 10.5) mg/d); Verapamil: N = 2 (mean = 170 (SD = 14.1) mg/d); Nifedipine: N = 3 (mean = 20 (SD = 0) mg/d); Furosemide: N = 8 (mean = 20 mg); Pantoprazole: N = 15 (mean =34.5 (SD = 20.9) mg); Antiemetics (except metoclopramide): N = 12; Haloperidol: N = 0; Promethazine: N = 0; Dimenhydramine: N = 1 (mean = 50 mg/d); Ondansetrone: N = 0; hypertension: N = 4; mild coronary heart disease: N = 6; pulmonary diseases: N = 1; history of cardiac arrhythmia: N = 2. Renal or hepatic impairment: N = 0. Sublingual buprenorphine: N = 5.

Interventions
Transdermal fentanyl v transdermal buprenorphine
If necessary, fast-acting formulations of the same drug were allowed (transdermal fentanyl group: 200 lg transmucosal fentanyl, transdermal buprenorphine group: 0.2 mg sublingual buprenorphine). No opioids other than the study opioids were permitted during the course of the study. No variation was allowed during the course of the observation period.

Outcomes
The occurrence of stool free periods >72 h, constipation, nausea, emesis, medication for symptom control, the use of analgesics and co-analgesics. The intensity of pain at rest, the intensity of nausea, and constipation was assessed once daily using the numerical rating scale (NRS, 0–10, 0 = no symptom, 10 = worst symptom imaginable). Patient mobility assessed by the ECOG Performance Status scale and items 1–5 of the EORTC questionnaire (EORTC QLQ 30, version 3) (1: not at all, 2: a little, 3: quite a bit, 4: very much; Item 1 ''Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?" Item 2 ''Do you have any trouble taking a long walk?" Item 3 ''Do you have any trouble taking a short walk out of the house?" Item 4 ''Do you need to stay in bed or in a chair during the day?"
Item 5 ''Do you need help with eating, dressing, washing yourself or using the toilet?")

Results *All of the statistical analyses performed by the authors were calculated on the present 2 groups and a third group of patients on oral hydromorphone using statistics appropriate for > 2 groups (such as ANOVA). These statistics are not reported as they are not targeted to the comparison of current interest.*
- Constipation: Transdermal fentanyl: Mean = 2.4 (SD = 3); transdermal buprenorphine: Mean = 2.2 (SD = 2.7)
- EORTC constipation item: Transdermal fentanyl: Mean = 2.1 (SD = 1.3); transdermal buprenorphine: Mean = 2.3 (SD = 1.3)
- Mean defecation rate: Transdermal fentanyl: Mean = .7 (SD = .6) 1/day; transdermal buprenorphine: Mean = .8 (SD = .6) 1/day
- Stool-free interval > 72 hours: Transdermal fentanyl: N = 12; transdermal buprenorphine: N = 13

- Use of laxatives: Transdermal fentanyl: N = 27; transdermal buprenorphine: N = 39
- Nausea: Transdermal fentanyl: Mean = 1.3 (SD = 2.2); transdermal buprenorphine: Mean = 1.2 (SD = 1.7)
- EORTC nausea item: Transdermal fentanyl: Mean = 1.8 (SD = 1.1); transdermal buprenorphine: Mean = 1.7 (SD = .9)
- Emesis: Transdermal fentanyl: Mean = .1 (SD = .3) 1/day, N = 9; transdermal buprenorphine: Mean = .1 (SD = .3) 1 day, N = 8
- EORTC emesis item: Transdermal fentanyl: Mean = 1.6 (SD = .9); transdermal buprenorphine: Mean = 1.4 (SD = .8)
- Use of anti-emetics: Transdermal fentanyl: N = 23; transdermal buprenorphine: N = 19
- Cumulative use of different substances: Transdermal fentanyl: N = 43; transdermal buprenorphine: N = 53
- Sodium picosulfate: Transdermal fentanyl: Mean = 11.5 (SD = 7.2) mg/day, N = 8; transdermal buprenorphine: Mean = 10 (SD = 0) mg/day, N = 9.
- Lactulose: Transdermal fentanyl: Mean = 18.8 (SD = 5.8) g/day, N = 11; transdermal buprenorphine: Mean = 16.3 (SD = 8.9) g/day, N = 9.
- Polyethylene glycol: Transdermal fentanyl: Mean = 20.7 (SD = 7.2) g/day, N = 12; transdermal buprenorphine: Mean = 21.8 (SD = 7) mg/day, N = 19.
- Paraffin: Transdermal fentanyl: N = 0; transdermal buprenorphine: N = 0.
- Bisacodyl: Transdermal fentanyl: N = 0; transdermal buprenorphine: Mean = 20 (SD = 14.1) mg/day, N = 2.
- **Metoclopramide**: Transdermal fentanyl: Mean = 22.5 (SD = 13.1) mg/day, N = 12; transdermal buprenorphine: Mean = 12.4 (SD = 6.5) mg/day, N = 14. *Doses are likely to be statistically significantly different between the groups*.

General comments
- Random selection of patients undergoing treatment with the target drugs, not random allocation to treatment
- Possible baseline differences
- The investigators checked daily whether the administration of all analgesics (opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, anticonvulsants), and adjuvants (laxatives, antiemetics) had been continued at the same dose levels.
- Not first-line

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

2d: Is subcutaneous morphine more effective than subcutaneous diamorphine or subcutaneous oxycodone as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable?

No evidence was identified for this review question

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

2e: Is subcutaneous opioid treatment more effective than transdermal patch treatment as first-line treatment for pain in patients with advanced and progressive disease who require strong opioids and for whom oral opioids are not suitable?

No evidence was identified for this review question

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

2f: What is the most effective opioid treatment for breakthrough pain in patients with advanced and progressive disease who receive first-line treatment with strong opioids (for background pain)?

Evidence table 5

Citation: Davies, A., Sitte, T., Elsner, F., Reale, C., Espinosa, J., Brooks, D., and Fallon, M. Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. Journal of Pain and Symptom Management 41[2], 358-366. 2011
Design: Multicenter, randomized, double-blind/double-dummy, crossover study **Country**: Europe and India **Aim**: To compare fentanyl pectin nasal spray (FPNS) to immediate-release morphine sulfate (IRMS) in patients with breakthrough cancer pain (BTCP).
Inclusion criteria 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 one to four episodes per day of moderate-severe BTCP.
Exclusion criteria Patients with uncontrolled or rapidly escalating background pain or whose conditions were medically unstable, or with a past inability to tolerate fentanyl or other opioids and any disorder or medication use likely to adversely affect normal functioning of the nasal mucosa.
Population N = 110, mean age at baseline = 55.9 ± 12.3 years (median age = 57 years).
Interventions The study consisted of four phases: (1) Screening phase (maximum 10 days), (2) Open dose titration phase (maximum 14 days; used to identify an effective FPNS dose between 100-800 mg/episode of target BTCP. Patients had to complete the dose-titration phase (titration to an effective dose of FPNS that successfully treated two consecutive BTCP episodes without unacceptable adverse events) to progress to the next phase. (3) Double-blind/double-dummy treatment phase (3-21 days; in which up to 10 BTCP episodes were treated (five treated with FPNS and encapsulated oral placebo, five with IRMS and nasal spray placebo). For all episodes, patients were instructed to take the oral treatment just before the nasal treatment. IRMS dose was determined for each patient as one-sixth the total daily oral morphine dose equivalent of the patient's background opioid medication or the patient's previously identified "effective" dose of IRMS for BTCP.), (4) End-of-treatment phase (1-14 days after the last dose).
Outcomes Pain intensity (measured on an 11-point numeric scale at baseline and at 5, 10, 15, 30, 45 and 60 minutes after dosing). Pain relief (measured on a 5-point numeric scale at 5, 10, 15, 30, 45 and 60 minutes after dosing). Adverse events, nasal assessments, patient satisfaction.
Results - 106/110 patients enrolled in the open dose titration phase took study medication and were included in the safety population. - 84 patients identified an effective and tolerable FPNS dose during the titration phase and were randomly assigned to double-blind treatment. - 6 and 5 patients withdrew from the titration phase because of lack of efficacy and adverse events, respectively. 79/84 patients randomly assigned completed the study. <u>Pain: Per-episode analysis (clinically meaningful pain relief defined as ≥ 2 point reduction in pain intensity):</u> - ≥ 2 point reduction in pain intensity (% of episodes): 5 min: FPNS (25.3%) = IRMS (22.8%); **10 min: FPNS (52.4%) > IRMS (45.4%); 15 min: FPNS (75.5%) > IRMS (69.3%);** 30 min: FPNS (86.8%) = IRMS (82.9%); 45 min: FPNS (89.2%) = IRMS (88.6%); 60 min: FPNS (91.4%) = IRMS (89.4%). - Pain relief score ≥ 2: 5 min: FPNS (20.2%) = IRMS (20.1%); 10 min: FPNS (39.4%) = IRMS (34.8%); **15 min: FPNS**

(60.2%) > IRMS (53.4%); 30 min: FPNS (82.4%) > IRMS (71.4%); 45 min: FPNS (87.4%) = IRMS (83.4%); 60 min: FPNS (91.3%) = IRMS (87.4%).
- Max total pain relief ≥ 33%: FPNS = IRMS at 10 mins; **FPNS > IRMS at 15, 30, 45 and 60 mins, i.e., significantly more episodes achieved max total pain relief of ≥ 33% after FPNS compared to IRMS.**
- Percentage of episodes requiring rescue medication: FPNS = IRMS

Patient acceptability (measured by 3 questions on 1-4 scale):
"How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?'':
"How satisfied are you with the speed of relief you gained with the nasal spray in the treatment of this episode of BTCP?''
"How satisfied are you with the reliability of the nasal spray you have used to treat this episode of BTCP?''
All 3 questions, the first 2 both at 30 and 60 mins and the latter at 60 mins, were rated more favourable for FPNS than for IRMS.

Adverse events and nasal tolerability:
- Treatment-emergent adverse events: 6 FPNS and 2 IRMS treatments (in 8 patients) resulted in discontinuation of study drug.
- No consistent patterns of reporting of nasal symptoms such as stuffy/blocked nose, runny nose, itching/sneezing, crusting/dryness of nose, burning/discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance and none of these nasal tolerability parameters were reported at an intensity of >2-3 (moderate or severe). FPNS = IRMS on all of these parameters.

General comments
- Double-blind/double-dummy controlled
- Modified intent-to-treat analysis including all patients in the randomized population who had treated at least one pain episode with each study medication (FPNS or IRMS) and had, for those episodes, a baseline and at least one subsequent pain intensity measurement. The safety population included all patients who had had ≥ 1 doses of FPNS.
- Drop-outs explained
- No correction for multiple analyses

References of Included Studies (For systematic reviews): NA

Citation: Vissers, D., Stam, W., Nolte, T., Lenre, M., Jansen, J., Vissers, Debby, Stam, Wiro, Nolte, Thomas, Lenre, Malin, and Jansen, Jeroen. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. Current Medical Research & Opinion 26[5], 1037-1045. 2010.

Design: Systematic review of RCTs w/ network meta-analysis
Country: International
Aim: To compare the efficacy of intranasal fentanyl spray (INFS), oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT) and immediate-release oral morphine (IRM) for the treatment of breakthrough cancer pain.

Inclusion criteria
RCTs on the management of breakthrough pain that allows comparison of INFS, FBT, OTFC and IRM in adult cancer patients suffering from breakthrough pain and treated with opioid analgesics for the management of background pain reporting pain intensity difference.

Exclusion criteria
None listed

Population
6 RCTs, 4 of which compared placebo to OTFC (Farrar et al., 1998), INFS (Kress et al., 2009), and FBT (Portenoy et al., 2006; Slatkin et al., 2007). The other 2 trials compared OTFC with IRM (Coluzzi et al., 2001 - *Also included in Zeppetella et al., 2009*) and INFS with OTFC (Mercadante et al., 2009).
The minimum episode frequency for inclusion in the INFS trials was 3 per week, and 1 for the other trials. The maximum episode frequency was 4 episodes per day for all trials. Pain intensity at the beginning of a breakthrough cancer pain episode and background opioid treatments were comparable across studies.
Coluzzi et al. (2001, *also included in Zeppetella et al., 2009*): N (double-blind phase) = 89; 47 males; mean age = 55 (SD = 11) years; number of treated episodes = NR for OTFC and IRM; mean pain intensity at time 0 = 6.9 for OFTC and 6.1 for IRM.
Farrar et al. (1998): N (double-blind phase) = 92; 41 males; mean age = 54 (SD = 12) years; number of treated episodes = 219 for placebo and 511 for OTFC; mean pain intensity at time 0 = 6 for placebo and 5.9 for OTFC.
Kress et al. (2009): N (double-blind phase) = 111; 56 males; mean age = 60.7 (SD = 9.1) years; number of treated episodes = 219 for placebo and 662 for INFS; mean pain intensity at time 0 = 6.4 (SD = 1.4) for placebo and 6.4 (SD = 1.3) for

INFS.
Mercadante et al. (2009): N (double-blind phase) = 139; 79 males; mean age = 62 (SD = 11.6) years; number of treated episodes = 577 for INFS and OTFC; mean pain intensity at time 0 = 6.4 (SD = 1.6) for INFS and 6.4 (SD = 1.5) for OTFC.
Portenoy et al. (2006): N (double-blind phase) = 77; 42 males; mean age = 57.5 (SD = 13.6) years; number of treated episodes = 208 for placebo and 493 for FBT; mean pain intensity at time 0 = 6.9 (SD = 0.2) for placebo and for FBT.
Slatkin et al. (2007): N (double-blind phase) = 86; 33 males; mean age = 53.9 (SD = 11.3) years; number of treated episodes = 223 for placebo and 493 for FBT; mean pain intensity at time 0 = 6.4 (SD = 1.7) for placebo and 6.4 (SD = 1.8) for FBT.

Interventions
INFS v OTFC v FBT v IRM:
First phase of each study consisted of an open-label dose titration phase to titrate each patient to successful dose before entry into double-blind phase for administration of a predetermined number of treatments containing either the intervention or placebo. FBT and OTFC patients were instructed to self-administer the entire dose within ca 15 mins.

Outcomes
Pain intensity difference at 15, 30, 45 and 60 mins measured on an 11-point scale (0 [no pain] – 10 [as bad as you can imagine]). The authors suggest that a ≥ 2-point reduction in pain intensity difference is associated with meaningful pain relief.

Results *Only the results relevant to the present PICO are reported*
Bayesian fixed effects mixed-treatment comparison (network meta-analysis):
Pain intensity difference: **INFS > IRM at 15 min (mean = 1.7, 95% credible interval (CrI) 1.1-2.3), 30 mins (mean = 1.4, 95% CrI 0.8-2.1), 45 mins (mean = 1.1, 95% CrI 0.5-1.7) and at 60 mins (mean = 0.9, CrI 0.2-1.6).**

General comments
No explicit search strategy included
Data extraction checked by 2nd reviewer
Cancer patients only

References of Included Studies (For systematic reviews):

- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al.Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Douleurs* 2002;**3**(1): 26–35.
- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al.Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001;**91**(1-2): 123–30.
- Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *Journal of the National Cancer Institute* 1998;**90**(8): 611–16.
- Kress HG, Oronska A, Kaczmarek, Z, et al. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microgram for breakthrough pain in patients with cancer: A phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Therapeut* 2009; **6**: 1177-91.
- Mercadante S, Radbruch L, Davies AN, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain – and opn-label, randomised, crossover trial. *Curr Med Res Opin* 2009; **25**: 2805-15.
- Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al.Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* 1999;**79**(2-3):303–12.
- Slatkin N, Xie F, Messina J, et al. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol* 2007; **7**: 327-34.

Citation: Zeppetella, Giovambattista and Ribeiro, Maria. Opioids for the management of breakthrough (episodic) pain in cancer patients. SO: Zeppetella Giovambattista, Ribeiro Maria DC.Opioids for the management of breakthrough (episodic) pain in cancer patients. Cochrane Database of Systematic Reviews: Reviews 2006 [1]. 2006. John Wiley & Sons, Ltd.

Design: Cochrane review w/o meta-analysis
Country: United Kingdom
Aim: To determine the efficacy of opioid analgesics given by any route, used for the management of breakthrough pain in patients with cancer, and to identify, and quantify, if data permit, any adverse effects of this treatment.

Inclusion criteria
All RCTs, blinded and non-blinded, published and unpublished, which compare opioid analgesics with placebo/other opioid analgesics/both/other active controls, given in any dose and by any mode of administration for the relief of breakthrough pain, in patients of all ages in any setting who are treated with opioids for cancer pain.

Exclusion criteria
None listed

Population
4 RCTs were included: 3 of which were not relevant to the current question (2 compared stating doses of oral transmucosal fentanyl citrate (OTFC; Christie et al., 1998; Portenoy et al., 1999) and 1 compared oral transmucosal fentanyl citrate with placebo (Farrar et al., 1998)). The 4th RCT compared OTFC with immediate-release morphine (IRM; Coluzzi et al., 2001) and the results of this RCT are the only results that are reported from this Cochrane review.

Coluzzi et al. (2001):
- N = 134 adult cancer out-patients from 19 American university and community-based hospitals and clinics using an oral opioid equivalent to 60-100 mg oral morphine per day or 50-300 mcg/h of fentanyl-TTS who had identified a successful dose of normal release morphine to treat their target breakthrough pain for at least three consecutive days.
- 93 patients were titrated to a successful OTFC dose (The commonest reasons for not completing the titration were protocol violation (N = 17 participants), adverse events (N = 14; in N = 5 adverse events were OTFC-related)).
- 89 of these 93 randomised patients used at least one set of study medication
- 47of these 89 patients were males, mean ±SD age of all participants = 55 ± 11 years and the commonest cancers were lung (N = 15), breast (N = 14), and colorectal (N = 13). Participants around the clock opioids included morphine (N = 43), transdermal fentanyl (N = 28), oxycodone (N = 14), methadone (N = 3), and hydrocodone (N = 1). Participants were using a variety of rescue medication, the commonest of which were morphine (N = 66), oxycodone (N = 11), hydrocodone (N = 4), and hydromorphone (N = 3), and propoxyphene (N = 1). The pathophysiology of target breakthrough pains was somatic (N = 46), visceral (N =25), neuropathic (N = 17), and unknown (N = 1).

Interventions
Coluzzi et al. (2001): OTFC v IRM:
Phase one of the study was an open label OTFC titration to determine the dose that successfully treated the target breakthrough pain with acceptable adverse effects. Participants were commenced on 200 mcg of OTFC and if more than one unit was required to successfully manage the pain a larger unit was used for subsequent pains. Once a successful dose was found participants entered phase two when they were given 10 pre-numbered oral transmucosal units and capsules; 5 contained the successful dose of OTFC with placebo capsules and 5 contained placebo oral transmucosal lozenge and the participants' pre-trial successful dose of immediate-release morphine capsules.

Outcomes
Coluzzi et al. (2001): Pain intensity (measured by 11-point rating scale), pain relief and global satisfaction (both measured by 5-point rating scale)

Results
Coluzzi et al. (2001):
- Jadad score 5/5; allocation concealment unclear.
- 75 patients treated at least one breakthrough pain with both OTFC and IRM (included in the primary efficacy analysis)
- 5 participants titrated to the 1600mcg dose without obtaining adequate relief.
- The mean ± SD IRM and OTFC doses for the 93 participants enrolled to the double-blind phase of the study were 31 ± 13.5mg and 811 ± 452mcg, respectively.
- There was no relationship between the normal release morphine and OTFC doses ($R^2 = 0.065$) or between the successful dose of rescue medication (IRM or OTFC) and around the clock oral or transdermal opioids.
- In the primary efficacy analysis OTFC was significantly superior to IRM in terms of pain intensity difference ($p<0.008$) and pain relief ($p < 0.009$) at 15, 30, 45 and 60 minutes, and global performance rating ($p<0.001$). *Descriptive data presented in graph form in original paper [not extracted]*.
- In addition, significantly ($p<0.001$) more pain episodes treated with OTFC had a > 33% change in pain intensity at 15 minutes than IRM.
- The most frequent reported adverse effects in 134 participants were somnolence (N = 20), nausea (N = 18), constipation (N = 14), and dizziness (N = 10). All adverse effects occurred during either OTFC titration or during double blind phase, at which time participants were receiving around the clock opioids, OTFC and IRM and it is therefore difficult to attribute an adverse effect specifically to OTFC or IRM.
- N = 18 withdrew from the study due to adverse effects, 6 of which were considered at least partly due to study medication.
- Percentage of breakthrough pains requiring additional rescue medication: OTFC = IRM.

General comments
- Comprehensive search (incl handsearch and search for unpublished data)
- Independent screening of studies for inclusion/exclusion by 2 reviewers
- Cancer patients only
- Quality of included studies assessed using the Jadad score

References of Included Studies (For systematic reviews):

- Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E, et al.Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *Journal of Clinical Oncology* 1998;**16**(10):3238–45.
- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al.Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Douleurs* 2002;**3**(1): 26–35.
- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al.Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001;**91**(1-2): 123–30.
- Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *Journal of the National Cancer Institute* 1998;**90**(8): 611–16.
- Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al.Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* 1999;**79**(2-3):303–12.

3.9 Management of constipation

Review question 3: What is the most effective management of side effects of strong opioids?

3a: 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?

No evidence was identified for this review question

3.10 Management of nausea

3b: 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?

No evidence was identified for this review question

3.11 Management of drowsiness

3c: Is opioid dose reduction or switching opioid more effective in reducing drowsiness in patients with advanced and progressive disease on strong opioids who experience drowsiness as a side effect?

No evidence was identified for this review question