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]

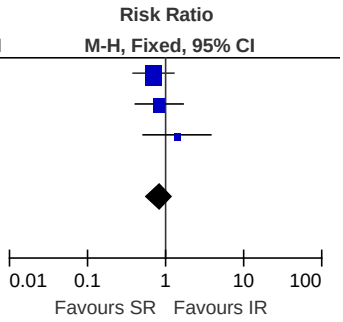
Forest plots of the results of review question 2a

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)

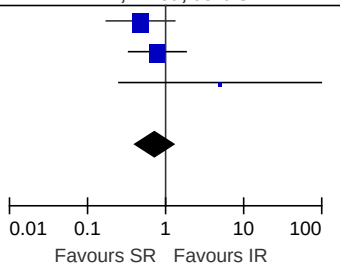


Dizziness

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)

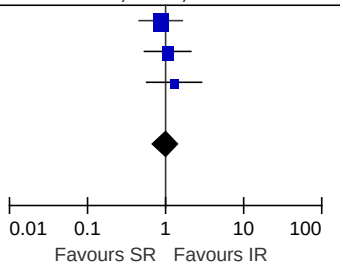


Drowsiness

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)

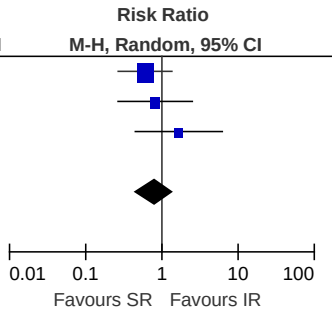


Vomiting

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)

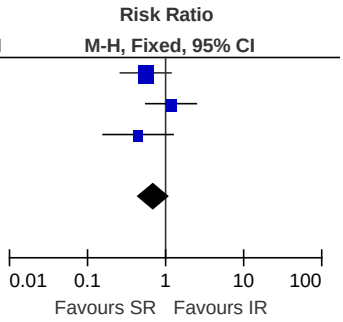


Constipation

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)

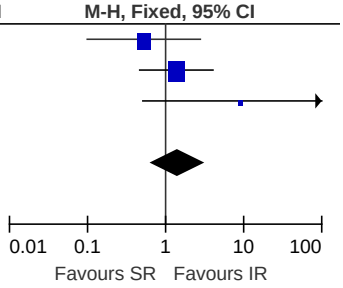


Pruritus

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)

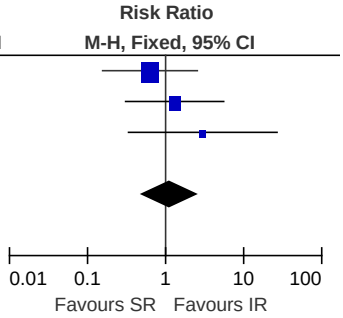


Dry mouth

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)

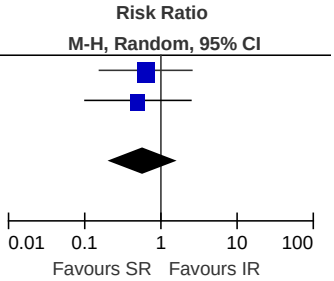


Nervousness

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)

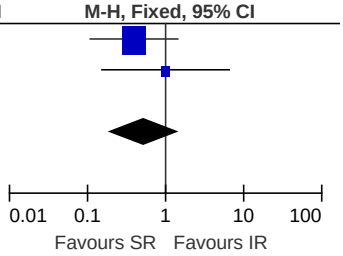


Asthenia

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)

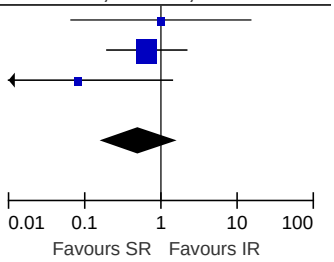


Headache

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)