

Evidence Profile 3.1. Modified-Release vs. Immediate-Release Morphine

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified Release Morphine	Immediate Release Morphine	Relative (95% CI)	Absolute (95% CI)		
Pain relief (categorical) (follow up: range 6 days to 14 days; assessed with VAS 0-100 [worst] <sup>A</sup> )												
4 <sup>1,2,3,4</sup>	RCT	serious <sup>B</sup>	not serious	not serious	not serious	none	108/111 (97.3%)	111/111 (100%)	RR 0.99 (0.95, 1.03)	27 more per 1000 (from 60 fewer to 4 more)	Moderate	CRITICAL
Pain relief (continuous) (follow up: range 24 hours to 14 days; assessed with VAS, PPI 0-100 [worst] <sup>A</sup> )												
4 <sup>5,6,7,8</sup>	RCT	not serious	not serious	not serious	serious <sup>C</sup>	none	77	73	Diff -0.6 (-5.9, 4.8)		Moderate	CRITICAL
Pain relief speed (achievement of stable pain control, follow up: 6 days)												
1 <sup>6</sup>	RCT	not serious	N/A	not serious	serious <sup>C</sup>	single study	19	15	Diff -0.4 days (-1.1, 0.3)		Low	IMPORTANT
Pain reduction maintenance												
0									not estimable			CRITICAL
Quality of life (follow up: 8 days; assessed with: EORTC; Scale: 0 to 100 [best])												
1 <sup>6</sup>	RCT	not serious	N/A	serious <sup>D</sup>	serious <sup>C</sup>	single study	19	15	Diff 9 (-6, 24)		Very Low	CRITICAL
Functional outcomes												
0									not estimable			CRITICAL
Adverse events: Sedation (follow up: range 2 days to 14 days; assessed with VAS 0-100 [worst] <sup>A</sup> )												
2 <sup>4,9</sup>	RCT	not serious	not serious	serious <sup>E</sup>	serious <sup>C</sup>	none	62	62	Diff 2.9 (-14.2, 8.5)		Low	IMPORTANT
Adverse events: Respiratory depression (follow up: range 2 days to 14 days)												
2 <sup>4,10</sup>	RCT	not serious	not serious	not serious	very serious <sup>F</sup>	no events	0/63 (0%)	0/63 (0%)	not estimable		Low	IMPORTANT

**Abbreviations:** CI: confidence interval; CR: controlled release; Diff: difference (between groups); EORTC: European Organisation for Research and Treatment of Cancer; IR: immediate release; N/A: not applicable; NS: not statistically significant; PPI: Present Pain Intensity; RCT: Randomized controlled trial(s); RR: Relative Risk (log scale); VAS: Visual Analog Scale.

Explanations

A. Scales transformed to 0 to 100, as necessary.

- B. Serious limitations related to lack of blinding and high attrition.
- C. Small sample size (and/or wide confidence interval).
- D. EORTC is a measure of quality of life that mixes concepts of both quality of life and functional outcomes.
- E. Not reporting of adverse event rates, per se, but sedation measured on scales.
- F. Small sample size and relative effect not estimable.

### *Trials*

1. Ventafridda, V., Saita, L., Barletta, L., Sbanotto, A., De Conno, F. Clinical observations on controlled-release morphine in cancer pain. *J Pain Symptom Manage*; Sep 1989.
2. Knudsen, J., Mortensen, S. M., Eikard, B., Henriksen, H. [Morphine depot tablets compared with conventional morphine tablets in the treatment of cancer pain]. *Ugeskr Laeger*; Feb 25 1985.
3. Gillette, J. F., Ferme, C., Moisy, N, et al. 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*; 1997.
4. Finn, J. W., Walsh, T. D., MacDonald, N., Bruera, E., Krebs, L. U., Shepard, K. V. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. *J Clin Oncol*; May 1993.
5. Thirlwell, M. P., Sloan, P. A., Maroun, J. A., et al. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer*; Jun 01 1989.
6. Klepstad, P., Kaasa, S., Jystad, A., Hval, B., Borchgrevink, P. C. Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a randomized, double-blind trial. *Pain*; Jan 2003.
7. Hanks, G. W., Twycross, R. G., Bliss, J. M. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. *Anaesthesia*; Aug 1987.
8. Arkinstall, W. W., Goughnour, B. R., White, J. A., Stewart, J. H. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. *Cmaj*; Mar 15 1989.
9. Walsh, T. D. Clinical evaluation of slow release morphine tablets. *Advances in Pain Research and Therapy*; 1985.
10. Cundiff, D., McCarthy, K., Savarese, J. J., et al. 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*; Jun 01 1989.