

Evidence-to-Decision table 3.1

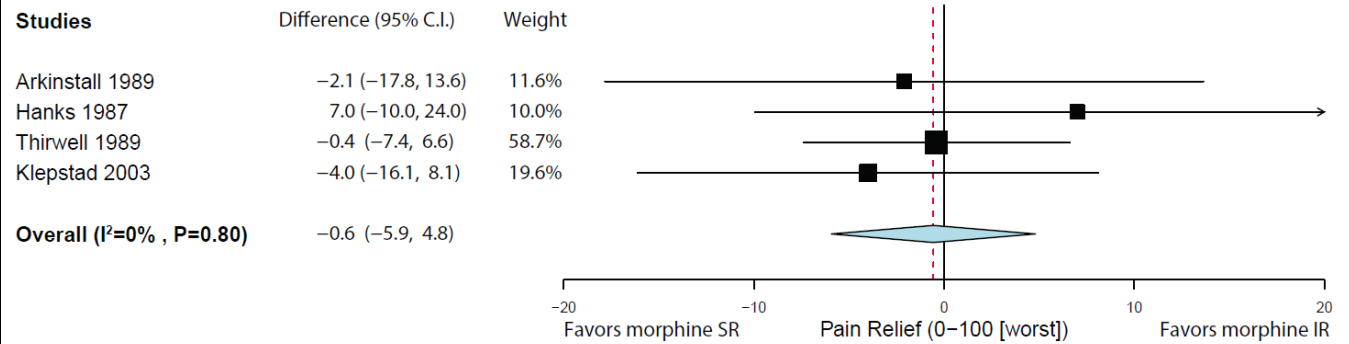
In adults (including older persons) and adolescents with pain related to active cancer, what is the evidence for the benefit of administering modified release morphine regularly as compared to immediate release morphine on a 4-hourly or as required basis, in order to maintain effective and safe pain control?

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	<p>Background:</p> <p>Clinical staff and patients are often faced with the options of administering modified-release morphine regularly or immediate-release morphine on a 4-hourly basis. There is some debate as to the importance of the differences between the medications^{64,65}</p> <p>Current WHO recommendation:</p> <p>The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. “The correct dose is the dose that works”, though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy.</p>
INTERVENTION:	Modified release morphine	
COMPARISON:	Immediate release morphine	
MAIN OUTCOMES:	<ul style="list-style-type: none"> • Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Respiratory depression (adverse event) 	
STRATIFICATIONS:	<ul style="list-style-type: none"> • Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain 	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	<p><u>Research Evidence</u> Global consumption of morphine in 2015 was 39.6 tonnes⁶⁶. Both immediate release and modified/extended/slow-release formulations are commonly used in clinical practice. Yet there is some debate as to the importance of the differences between the medications^{64,65}.</p> <p><u>Additional considerations</u> WHO should, if possible, provide evidence based guidance on the matter.</p>

The choice of modified-release and immediate-release morphine probably makes little or no difference to pain relief and may make no difference to pain relief speed, maintenance of pain relief, and sedation. Respiratory distress events may be rare with both formulations.

Forest Plot 3.1. Pain Relief (Continuous Scale) Modified-Release vs. Immediate-Release Morphine



Abbreviation: *CI: confidence interval.*

Scores from individual studies have been transformed to a uniform 0-100 scale (100 = worst).

ACCEPTABILITY & PREFERENCES	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Major variability <input checked="" type="checkbox"/> Yes</p> <p>Minor variability <input type="checkbox"/></p> <p>Uncertain <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p><u>Research Evidence</u> None</p> <p><u>Additional considerations</u> The GDG identified reasons for variability in patient preferences from clinical experience. Some patients prefer modified release morphine because of the lower pill burden, more even analgesia, and less waking at night. Other patients, however, may prefer a higher pill burden for psychological reasons. In other patients still there may be stigma against certain formulations. This indicates major variability.</p> <p>The GDG deemed variability in clinicians preferences between the two formulations to be minor, considering there to be no strong reasons for a clinician or other key stakeholder to prefer one over the other.</p>
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How large are the resource requirements?

Major Minor Yes Uncertain

Is the option feasible to implement?

Yes No Uncertain

Research Evidence

Source: ¹²	Number of Countries Where Available for Free	Number of Countries Where Available	Price of one 30-Day Opioid Treatment			
			Median	IQR	Mean	SD
Morphine oral immediate release (tablet, capsule)	11	35	\$ 49.70	\$ 80.50	\$ 78.50	\$ 92.00
Morphine oral slow release (tablet, capsule)	15	44	\$ 56.80	\$ 110.50	\$ 83.80	\$ 90.70
Morphine oral (liquid)	9	26	\$ 41.90	\$ 96.50	\$ 67.58	\$ 63.60
Morphine injectable (ampoule)	19	49	\$ 88.50	\$ 167.30	\$ 167.20	\$ 225.30
Fentanyl (transdermal patch)	15	47	\$ 81.20	\$ 263.40	\$ 144.60	\$ 154.10
Methadone oral solid (tablet, capsule)	9	22	\$ 26.50	\$ 38.30	\$ 40.50	\$ 29.10
Methadone oral (liquid)	9	26	\$ 13.10	\$ 70.90	\$ 58.80	\$ 103.40
Oxycodone oral immediate release (tablet, capsule)	6	19	\$ 202.90	\$ 156.80	\$ 198.10	\$ 125.20
Oxycodone oral slow release (tablet, capsule)	6	21	\$ 237.20	\$ 473.70	\$ 312.40	\$ 252.10
Hydromorphone oral immediate release (tablet, capsule)	2	7	\$ 103.45	\$ 115.60	\$ 78.30	\$ 61.50
Hydromorphone oral slow release (tablet, capsule)	3	10	\$ 14.97	\$ 89.10	\$ 51.60	\$ 54.90
Hydromorphone oral (liquid)	0	2	\$ 146.20	NA	\$ 150.30	\$ 146.20
Hydromorphone injectable (ampoule)	2	4	\$ 101.10	NA	\$ 73.20	\$ 101.10

		<p><u>Additional considerations</u> Typically, modified release formulations are more expensive per dose. It is not clear which formulation is more cost effective.</p>
	<p>Would the option improve equity in health?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain</p>	<p><u>Research Evidence</u> None</p> <p><u>Additional considerations</u> Modified release morphine is typically more expensive and its use probably makes little to no difference to pain relief, pain relief speed, maintenance of pain relief, and sedation. The GDG noted the problem that in many settings, especially some low income ones, only modified release morphine is available where a faster release morphine is necessary for breakthrough pain relief. They reported that in some settings, clinical staff are forced to crush up modified release medication in order to make it release more quickly, since immediate release morphine is not available. On occasion, injectable immediate release morphine is available, but this is less appropriate for outpatients. Ensuring that both modified- and immediate-release morphine is available in an oral formulation would increase equity.</p>

Recommendation**Current recommendation:**

The 1996 WHO Guidelines discuss the options of a 4-hourly regimen of morphine or slow-release morphine tablets every 12 hours. “The correct dose is the dose that works”, though it states that in most patients, pain is controlled with 10-30mg every four hours. Slow release morphine tablets vary in strength between 10mg to 200mg. The analgesic should be given at regular time intervals, not merely when the patient complains of pain. The use of morphine should be dictated by intensity of pain, not by life expectancy.

New (draft) recommendation:

Regularly-dosed immediate-release oral morphine, or regularly-dosed slow-release morphine should be used for pain relief. With either formulation, immediate-release oral morphine should be used as rescue medication.

Strength of Recommendation**Strong**

Quality of Evidence

- **MODERATE**
[Pain (critical) = moderate (pain relief), low (pain score)
Pain relief speed (important) = low
Pain reduction maintenance (critical) = low
Sedation (adverse event) (important) = low
Other outcomes omitted for no data or inconclusive findings]
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Justification

Modified release morphine is typically more expensive and its use probably makes little to no difference to pain relief, pain relief speed, maintenance of pain relief, and sedation. Yet patients sometimes place high option value on the availability of both formulations. The GDG therefore felt that having both modified- and immediate-release morphine available in an oral formulation would be preferred, and either regimen (modified-release for pain relief maintenance with immediate release as rescue medication or immediate-release used for both) could be used. They noted that if a health system must choose between one or the other formulation, immediate-release oral morphine should be chosen as it can be used as both maintenance and rescue medication whereas modified release morphine cannot. The GDG complained that in many settings, especially some low- and middle-income ones, only modified release morphine is available, where a faster release morphine is necessary for breakthrough pain relief. They reported that in some settings, clinical staff are forced to crush up modified release medication in order to make it release more quickly, since immediate release morphine is not available. On occasion, injectable immediate release morphine is available, but this is less appropriate for outpatients.

The text of the guidelines explains that the regularity of dosing should depend on clinical assessment and the recommendation applies only if the decision to use morphine has been made.

Subgroup considerations

**Implementation considerations
[incl. M&E]**

Research priorities
