<table>
<tr><td colspan="3">Evidence-to-Decision table 1.3</td></tr>
<tr><td colspan="3">In adults (including older persons) and adolescents with pain related to active cancer receiving first-line treatment with opioids for background pain, what is the most effective opioid treatment for breakthrough pain?</td></tr>
<tr><td>POPULATION:</td><td>Adults (including older persons) and adolescents with cancer-related pain</td><td rowspan="7">Background:<br><br>Cancer was responsible for 8.8 million deaths in 2015[7]. The prevalence of breakthrough pain in adult populations with cancer is reported to be almost 60%[53].<br><br>Current WHO recommendation:<br>In addition to normal doses in a regiment of analgesics given for cancer pain relief, rescue doses for incident (intermittent) and breakthrough pain should be given that are 50-100% of the regular four hourly dose.</td></tr>
<tr><td>INTERVENTION:</td><td>Opioids</td></tr>
<tr><td>COMPARISON:</td><td>Other opioids</td></tr>
<tr><td>MAIN OUTCOMES:</td><td>• Pain relief<br>• Pain relief speed<br>• Pain relief maintenance<br>• Quality of life (QoL)<br>• Functional outcomes<br>• Respiratory depression (adverse event)<br>• Confusion (adverse event)</td></tr>
<tr><td>STRATIFICATIONS:</td><td>• Age (adults, older persons, adolescents, children)<br>• History of substance abuse<br>• Refractory pain</td></tr>
<tr><td>SETTING:</td><td>All</td></tr>
<tr><td>PERSPECTIVE:</td><td>Population</td></tr>
</table>

| | CRITERIA | SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| PROBLEM | **Is the problem a priority?**<br>Yes | Cancer was responsible for 8.8 million deaths in 2015[7]. Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of people dying from cancer experience moderate or severe pain lasting on average 90 days[6]. A recent systematic review of published evidence reports a similarly high figure that 66.4% of patients with advanced, metastatic, or terminal disease experience pain[52]. The prevalence of breakthrough pain in adult populations with cancer is reported to be almost 60%[53]. |

| | | |
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| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable effects?**<br><br>Yes: ☐ No: ☐ Uncertain: Yes | • **One randomized controlled trial** compared analgesics specifically for management of breakthrough pain. It was conducted in a population of older persons varied cancer types. Studies that only compared a medication with placebo were excluded.<br><br>**BENEFITS and HARMS**<br>• **One trial** provided **low strength of evidence** that the choice between **sustained-release and immediate-release morphine may make no difference to prevent breakthrough pain** (RR 1.00; 95% CI 0.75, 1.33) or to **reduce pain** (summary difference on a 0 to 100 [best] scale = -0.2; 95% CI -1.0, 0.6).<br>• **No trial** reported on **pain relief speed**.<br>• **No trial** reported on **pain relief maintenance**.<br>• **No trial** reported on **QoL**.<br>• **No trial** reported on **functional outcomes**.<br>• **No trial** reported on **respiratory depression.**<br>• Based on **one trial** that provided **very low strength of evidence**, we are uncertain about differences between **sustained-release and immediate-release morphine** to avoid **confusion.**<br><br>**STRATIFICATIONS**<br>• Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons.<br>• Studies provide no data regarding history of substance abuse.<br>• Studies provide no data regarading refractory pain.<br><br>**SUMMARY**<br>There may be no difference in likelihood of breakthrough pain or overall pain relief between sustained-release and immediate-release morphine. |

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| **ACCEPTABILITY & PREFERENCES** | **Is there important uncertainty or variability about how much people value the options?**<br>Major variability<br>[ ]<br>Minor variability<br>[ ]<br>Uncertain<br>[Yes]<br>**Is the option acceptable to key stakeholders?**<br>Yes [ ] No [ ] Uncertain [Yes] | **Research Evidence**<br>None<br><br>**Additional considerations**<br>None |

**FEASIBILITY ./ RESOURCE USE**

**How large are the resource requirements?**

Major ☐ Minor ☐ Uncertai Yes

**Is the option feasible to implement?**

Yes ☐ No ☐ Uncertain Yes

| 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 |

**Additional considerations**

| | | |
|---|---|---|
| | | The GDG noted that while no recommendation would be made for this PICO (instead a best practice statement would be made), it was worth highlighting that the cost of certain formulations, such as sublingual fentanyl, were likely to be prohibitively expensive for some low- and middle-income settings. |
| | **Would the option improve equity in health?**<br><br>Yes ☐ No ☐ Uncertai Yes | **Research Evidence**<br>None<br><br>**Additional considerations**<br>None |

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| **Recommendation** | **Current recommendation:**<br>In addition to normal doses in a regiment of analgesics given for cancer pain relief, rescue doses for incident (intermittent) and breakthrough pain should be given that are 50-100% of the regular four hourly dose.<br><br>**New (draft) recommendation:**<br>None. |
| **Strength of Recommendation** | |
| **Quality of Evidence** | ➢ **Low**<br>[Pain (critical) = low (one medication comparison)<br>others omitted for no or inconclusive data] |
| **Justification** | The GDG felt that they could not justify making a recommendation on the basis of only one eligible low quality RCT that looked at too few of the options available clinically. The task of systematically reviewing the question was also confounded by differing definitions of breakthrough pain across trials.<br><br>The GDG opted instead for a best practice statement on the matter because the GDG felt that, in the interests of patients, WHO should not remain silent on the issue. |
| **Subgroup considerations** | |
| **Implementation considerations [incl. M&E]** | |
| **Research priorities** | |