Evidence-to-Decision table 1.2

In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between opioids for maintenance of therapy in order to achieve rapid, effective and safe pain control?

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain
INTERVENTION:	Opioids
COMPARISON:	Opioids, placebo Multiple comparisons
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Respiratory depression (adverse event) • Sedation (adverse event)
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain
SETTING:	All
PERSPECTIVE:	Population

For full analysis, please see Annex 6 for the Network Meta Analysis which primarily addresses this question

Background:

- Recent estimates state that 25.5 million people died in 2015 in serious health-related suffering, of which 80% lived in countries that lack access to palliative care and pain relief [6]. 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].

Current WHO recommendation:

- Analgesics should be given "by the mouth", "by the clock", "by the ladder", "for the individual", with "attention to detail".
    - By the mouth – Where possible, analgesics should be given by the mouth. Rectal suppositories (or alternatively, continuous subcutaneous infusion) may be preferred in patients with dysphagia , uncontrolled vomiting, or gastrointestinal obstruction.
    - By the clock – Analgesics should be given at fixed intervals of time. The dose should be gradually increased until the patient is comfortable. The next dose should be given before the effect of the previous dose has worn off.
    - By the ladder – "The first step is a non-opioid. If this does not relieve the pain, an opioid for mild to moderate pain should be added. When an opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, an opioid for moderate to severe pain should be substituted. Only one drug from each of the groups should be used at the same time. Adjuvant drugs should be given for specific indications. If a drug ceases to be effective, do not switch to an alternative drug of similar efficacy … but prescribe a drug that is definitely stronger."
    - For the individual – The right dose is the dose that relieves the patient's pain.
    - With attention to detail – The first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally, the patient's analgesic medication regimen should be written out in full for the patient and their family to work from.
- Previous guidelines recommend that dose takes into account the associated development of tolerance and possible development of physical dependence. Tolerance is characterized by decreased efficacy and

		duration of action of the opioid medication with repeated administration, requiring an increased dose to maintain the analgesic effect. It states that in practice, physical dependence and tolerance do not prevent the effective use of these medications. Patients with stable disease often remain on a stable dose for weeks or months. Previous guidelines discount the development of psychological dependence in cancer patients as a result of receiving opioids for relief of pain. The guidelines also recommend that the regimen offered accounts for disease-induced alterations in opioid pharmacokinetics, especially in cirrhosis and renal failure. If a patient appears to be intolerant to morphine, an alternative strong opioid is recommended. • Choice of analgesic – The array of specific non-opioids considered included acetylsalicylic acid (ASA) 500-600mg every 4-6 hours, other NSAIDs (such as those on essential medicines lists, e.g. ibuprofen 400mg every 4-6 hours and indomethacin 25mg every 6 hours), and paracetamol 650-1000mg every 4-6 hours. Specific choice from this selection "will depend on factors such as local availability and cost." The guidelines take note of typical contraindications such as gastric irritation, toxicities, hypersensitivity reactions, and other potential adverse effects of these medications, and notes the maximum dosages for each of the medications to avoid excess adverse effects: maximum 4g of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg indomethacin per day. The 1996 guidelines state that the initial dose of an opioid for moderate to severe pain depends mainly on the patient's previous medication. For those who have previously received 60-100mg of codeine by mouth, they state that a starting dose of 10-15mg of morphine is usually adequate. Dose should be halved if the patient becomes somnolent after the first dose and is free of pain. If after 24 hours on this medication, Not all medications were discussed with regards the maintenance of pain management. Dosages for medications should be increased according to clinical assessment. The recommended starting regimens for each medication discussed are: • Codeine by mouth 30-120mg every four hours. • Morphine by simple aqueous solution or tablet every four hours, or by slow release tablets every 12 hours. The correct dose is "the dose that works" to relieve a patient's pain. Typical starting dose 10-15mg. • Standardised opium – no standard dose given. • Tramadol usual dose by mouth 50-100mg every 4-6 hours. • Hydromorphone usual starting dose 1-2mg by mouth or 1mg by subcutaneous injection, analgesia lasting 3-4 hours. Doses of hydromorphone by injection are typically 1/3 to ½ of the previously satisfactory oral dose. • Methadone 5-10mg by mouth or by subcutaneous injection, analgesia lasting 6-12 hours. • Levorphanol usual starting dose 1-2mg by mouth four times per day. Half dose for injection. • Pethidine 50-100mg may be given every three hours as a starting dose, or more frequently in patients with severe cancer pain.

		• Oxycodone usual starting dose 5-15mg by mouth or rectally, analgesia lasting 3-5 hours. • Buprenorphine dose to account for its 60 times greater potency than orally administered morphine. When pain is no longer controlled by buprenorphine, 100 times the previously administered total daily dose of buprenorphine should be given of oral morphine sulfate in a four hourly regimen instead. It states that most patients' pain is satisfactorily controlled on an 8 hour regimen. • Night doses – medications should be given through the night or in a larger dose at bedtime to sustain the plasma level of the medication within the effective range. Many patients with a double dose of morphine do not need a further dose until morning. A double dose is not necessary with slow release preparations of morphine or with longer0acting medications such as methadone and buprenorphine.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	Expert opinion and data from country experiences from several low-income countries suggest that approximately 80% of the millions of people dying from cancer each year experience moderate or severe pain lasting on average 90 days, most of whom lived in countries with inadequate access and availability of adequate pain management[6]. Previous WHO guidelines were issued in 1996. Up to date guidance is needed in order to overcome attitude and knowledge barriers to the delivery of adequate pain management.[9]

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes No Uncertain Yes	Thirty-eight trials provided data for outcomes of interest. **Readers are encouraged to refer to Annex 6 Network Meta Analysis (NMA) for further analysis on the 'effective pain relief' outcome** For the direct evidence, 27 randomized controlled trials compared analgesics with either other analgesics or placebo (which were all analyzed together); 26 of these compared analgesics to each other. The trials evaluated 14 classes of analgesics (high-potency opioid, high-potency opioid + antidepressant, high-potency opioid + NSAID, low-potency opioid, high-potency opioid + opioid antagonist, high-potency opioid + paracetamol, low-potency opioid + NSAID, low-potency opioid + paracetamol, high-potency opioid + low-potency opioid, NSAID, NSAID + antidepressant, cannabinoid, and other non-opioid analgesic). 12 studies were conducted in older persons, no study was conducted in only adolescents. **BENEFITS and HARMS** • Direct and indirect evidence from the NMA of **6 trials** provide **low strength of evidence** that the following analgesic classes **may make no difference to pain relief** than the alternative: ○ **Low-potency opioid** may be no better than **low-potency opioid + paracetamol** (OR 1.40; 95% CI 0.55, 3.55) ○ **High-potency opioid + paracetamol** may be no better than **low-potency opioid + paracetamol** (OR 1.25; 95% CI 0.51, 3.09) ○ **High-potency opioid + paracetamol** may be no better than **low-potency opioid** (OR 0.89; 95% CI 0.35, 2.27) All other comparisons have very low strength of evidence. • Direct and indirect evidence from the NMA of **13 trials** provide **high strength of evidence** that **high-potency opioid + NSAID reduces pain better** than: ○ **High-potency opioid + opioid antagonist** (SMD -1.16; 95% CI -1.90,-0.41) ○ **Non-opioid analgesic (dipyrone)** (SMD -1.16; 95% CI -1.72, -0.60) ○ **High-potency opioid (alone)** (SMD -0.96; 95% CI -1.36, -0.56) There is **moderate strength of evidence** for **reducing pain** regarding comparisons of the following analgesic classes: ○ **High-potency opioid + NSAID** is **probably better** than **high-potency opioid + low-potency opioid** (SMD -0.83; 95% CI -1.28, -0.37) ○ **High-potency opioid + NSAID** is **probably better** than **cannabinoid** (SMD -0.77; 95% CI -1.43, -0.10) ○ **Cannabinoid** is **probably no better** than **non-opioid analgesic (dipyrone)** (SMD -0.39; 95% CI -1.06, 0.27) ○ **NSAID (alone)** is **probably no better** than **NSAID + antidepressant** (SMD -0.37; 95% CI -0.81; 0.06) ○ **Non-opioid analgesic (dipyrone)** is **probably no better** than **high-potency opioid** (SMD 0.20; 95% CI -0.20, 0.59) There is **low strength of evidence** for **reducing pain** regarding comparisons of the following analgesic classes: ○ **High-potency opioid + NSAID may be better** than **low-potency opioid** (SMD -0.73; 95% CI -1.29, -0.18) ○ **Low-potency opioid may be no better** than **non-opioid analgesic (dipyrone)** (SMD -0.43; 95% CI -0.98, 0.13) ○ **Cannabinoid may be no better** than **high-potency opioid + opioid antagonist** (SMD -0.39; 95% CI -1.22, 0.44) ○ **High-potency opioid + low-potency opioid may be no better** than **non-opioid analgesic (dipyrone)** (SMD -0.33; 95% CI -0.79, 0.12)

- **NSAID + antidepressant** may be no better than **Low-potency opioid + NSAID** and (SMD 0.09; 95% CI -0.34, 0.52)

The evidence for the choice between the following analgesic classes was **very low:**

- **High-potency opioid** and **high-potency opioid + opioid antagonist** (SMD -0.20; 95% CI -0.83, 0.44)
- **Cannabinoid** and **high-potency opioid** (SMD -0.19; 95% CI -0.73, 0.34)
- **High-potency opioid + low-potency opioid** and **high-potency opioid** (SMD -0.13; 95 CI -0.36, 0.09)
- **Low-potency opioid + NSAID** and **high-potency opioid + low-potency opioid** (SMD -0.12; 95% CI -0.73, 0.49)
- **NSAID + antidepressant** and **NSAID + low-potency opioid** (SMD -0.09; 95% CI -0.52, 0.34)
- **Low-potency opioid** and **cannabinoid** (SMD -0.03; 95% CI -0.52, 0.45)
- **Non-opioid analgesic (dipyrone)** and **high-potency opioid + opioid antagonist (dipyrone)** (SMD 0.00; 95% CI -0.74, 0.75)

- From direct evidence, f**our trials** provided **low strength of evidence** of **no significant difference on speed of pain relief** among Codeine, Codeine + Ibuprofen, Diclofenac, Ketorolac, Morphine CR, Morphine IR, and Oxycodone CR. The studies evaluated different outcomes, which ranged from minutes to days.
- **Four trials** provided **low strength of evidence** of **no significant differences of duration of maintenance of pain reduction among the interventions** (Codeine, Codeine + Ibuprofen, Diclofenac, Kadian (every 12 hours), Ketorolac, Morphine CR, and Morphine IR). One trial reported that Kadian every 24 hours had longer mean time to remedication (16 hr) than Kadian every 12 hours (9.1 hr) or Morphine CR (8.7 hr).
- **No trial** reported on **quality of life**.
- **Two trials** provided **low strength of evidence** of **no significant difference for functional outcomes** between Morphine and Methadone (on the Karnofsky Performance Scale), but favoring Ketorolac over Dexketoprofen trometamol.
- **One trial** provided **very low strength of evidence** reported on respiratory depression, **reporting a single occurrence** of "respiratory failure" among 62 people taking tapentadol, but none with morphine SR.
- **Seventeen trials** provided **very low strength of evidence** reported on sedation, using various definitions within studies (sedation, somnolence, drowsiness, tiredness). **The rates of sedation were heterogeneous across 10 interventions**: Fentanyl TD (3 trials) 6-14%, Hydromorphone CR (1 trial) 7%, Methadone (2 trials) 15-27%, Morphine CR (6 trials) 6-19%, Morphine IR (3 trials) 17-70%, Oxycodone CR (1 trial) 59%, Oxycodone IR (2 trials) 32-65%, Tapentadol (1 trial) 4%, Tramadol + Fentanyl TD (1 trial) 6%, Tramadol + Tapentadol (1 trial 9%). **Two trials** provided **low strength of evidence** comparing risk of sedation between **fentanyl and morphine SR** yielding a RR of 0.88 (95% CI 0.52, 1.48), **nominally favoring fentanyl**.

STRATIFICATIONS

- Stratification of the analysis of all analgesics separate for adolescents and older persons provided very uncertain results for pain relief (due to the small number of studies) which however appear to be in line with the findings from the analysis of all studies
- Studies provide no data regarding history of substance abuse or refractory pain.

SUMMARY

		Combination high-potency opioid and NSAID reduces pain better than alternative analgesics. Choice of analgesic may make little or no difference in speed of pain relief, duration of maintenance of pain reduction, or functional outcomes. Fentanyl may cause slightly less sedation than sustained-release morphine.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [Yes] No [ ] Uncertain [ ]	**<u>Research Evidence:</u>** The systematic review reveals some differences between the medications with regards to adverse effects. The GDG agreed that all options should be acceptable to key stakeholders such as clinicians and policymakers, but ill-founded opiophobia continues to be an issue with acceptability in many settings worldwide[11]. **<u>Additional considerations</u>** The GDG acknowledged that some patients will prefer some medications over others due to differences in adverse event profiles or contraindications for certain medications. To match this important preference, the GDG implored that there be a variety of appropriate treatments available to patients to meet their variegated clinical needs, including at least one fast acting strong opioid medication. However, the GDG also acknowledged that many differences between opioid medications are often overstated, as evidenced by the guidelines' systematic review. Therefore the cost of medications should be an important factor in decisions to make certain medications available. In low-resource settings, cheaper medications should be preferred as the clinical differences between those and the more expensive medications are small.

FEASIBILITY ./ RESOURCE USE

How large are the resource requirements?

Major	Minor	Uncertain
	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

	Would the option improve equity in health? Yes No Uncertain Yes ☐ ☐	**<u>Research evidence</u>** None presented. **<u>Additional considerations</u>** The GDG believe that the availability of these options to patients would increase equity since the majority of the world's population has poor access and availability to the medications. The GDG note that in many countries, only the capital city has access and availability for some patients; in the rest of the country, these medications may be unavailable. Furthermore, they note that since there is variation in patients' response to specific analgesic medications, there should be multiple medications available that are appropriate for all pain intensities. Improvements in equity are contingent on multiple factors, including the availability of affordable medications. The GDG reiterated their view that cheap, effective medications should be available to all patients in need of pain management and if there is no obvious best analgesic for a patient, the cheapest medication should be used. The GDG also bore in mind the risk of unintended consequences. They noted that balanced regulations of these strong analgesics, which balance the necessity of their availability to patients who need them with the necessity of tackling their misuse, are possible. Recommendations on how to achieve this balance are presented in other WHO documents[13].

Recommendation

Current recommendation:

- Analgesics should be given "by the mouth", "by the clock", "by the ladder", "for the individual", with "attention to detail".
    - By the mouth – Where possible, analgesics should be given by the mouth. Rectal suppositories (or alternatively, continuous subcutaneous infusion) may be preferred in patients with dysphagia , uncontrolled vomiting, or gastrointestinal obstruction.
    - By the clock – Analgesics should be given at fixed intervals of time. The dose should be gradually increased until the patient is comfortable. The next dose should be given before the effect of the previous dose has worn off.
    - By the ladder – "The first step is a non-opioid. If this does not relieve the pain, an opioid for mild to moderate pain should be added. When an opioid for mild to moderate pain in combination with a non-opioid fails to relieve the pain, an opioid for moderate to severe pain should be substituted. Only one drug from each of the groups should be used at the same time. Adjuvant drugs should be given for specific indications. If a drug ceases to be effective, do not switch to an alternative drug of similar efficacy … but prescribe a drug that is definitely stronger."
    - For the individual – The right dose is the dose that relieves the patient's pain.
    - With attention to detail – The first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally, the patient's analgesic medication regimen should be written out in full for the patient and their family to work from.
- Previous guidelines recommend that dose takes into account the associated development of tolerance and possible development of physical dependence. Tolerance is characterized by decreased efficacy and duration of action of the opioid medication with repeated administration, requiring an increased dose to maintain the analgesic effect. It states that in practice, physical dependence and tolerance do not prevent the effective use of these medications. Patients with stable disease often remain on a stable dose for weeks or months. Previous guidelines discount the development of psychological dependence in cancer patients as a result of receiving opioids for relief of pain. The guidelines also recommend that the regimen offered accounts for disease-induced alterations in opioid pharmacokinetics, especially in cirrhosis and renal failure. If a patient appears to be intolerant to morphine, an alternative strong opioid is recommended.
- Choice of analgesic – The array of specific non-opioids considered included acetylsalicylic acid (ASA) 500-600mg every 4-6 hours, other NSAIDs (such as those on essential medicines lists, e.g. ibuprofen 400mg every 4-6 hours and ~~indometacin~~indomethacin 25mg every 6 hours), and paracetamol 650-1000mg every 4-6 hours. Specific choice from this selection "will depend on factors such as local availability and cost." The guidelines take note of typical contraindications such as gastric irritation, toxicities, hypersensitivity reactions, and other potential adverse effects of these medications, and notes the maximum dosages for each of the medications to avoid excess adverse effects: maximum 4g of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg ~~indometacin~~indomethacin per day.

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Not all medications were discussed with regards the maintenance of pain management. Dosages for medications should be increased according to clinical assessment. The recommended starting regimens for each medication discussed are:

- Codeine by mouth 30-120mg every four hours.
- Morphine by simple aqueous solution or tablet every four hours, or by slow release tablets every 12 hours. The correct dose is "the dose that works" to relieve a patient's pain. Typical starting dose 10-15mg.
- Standardised opium – no standard dose given.
- Tramadol usual dose by mouth 50-100mg every 4-6 hours.
- Hydromorphone usual starting dose 1-2mg by mouth or 1mg by subcutaneous injection, analgesia lasting 3-4 hours. Doses of hydromorphone by injection are typically 1/3 to ½ of the previously satisfactory oral dose.
- Methadone 5-10mg by mouth or by subcutaneous injection, analgesia lasting 6-12 hours.
- Levorphanol usual starting dose 1-2mg by mouth four times per day. Half dose for injection.
- Pethidine 50-100mg may be given every three hours as a starting dose, or more frequently in patients with severe cancer pain.
- Oxycodone usual starting dose 5-15mg by mouth or rectally, analgesia lasting 3-5 hours.
- Buprenorphine dose to account for its 60 times greater potency than orally administered morphine. When pain is no longer controlled by buprenorphine, 100 times the previously administered total daily dose of buprenorphine should be given of oral morphine sulfate in a four hourly regimen instead. It states that most patients' pain is satisfactorily controlled on an 8 hour regimen.

- Night doses – medications should be given through the night or in a larger dose at bedtime to sustain the plasma level of the medication within the effective range. Many patients with a double dose of morphine do not need a further dose until morning. A double dose is not necessary with slow release preparations of morphine or with longer0acting medications such as methadone and buprenorphine.

New (draft) recommendation:
In adults (including the older person) and adolescents with pain related to active cancer, any opioid may be considered for maintenance of pain relief, depending on clinical assessment and pain severity, in order to achieve rapid, effective and safe pain control
(Strong recommendation; low quality)

The choice of analgesic medication, dosage, and timing should take into the specific pharmacokinetics of each opioid medication, their contraindications, and their adverse effects in different patients.

Strength of Recommendation	**Strong**

Quality of Evidence	➢ **Low (Mixed)** [Pain (critical) = moderate to high for combination high-potency opioid + NSAID. Low to moderate for other scattered comparisons. See network meta analysis for further delineation of the quality of evidence for this outcome. Pain reduction maintenance (critical) = low Pain relief maintenance (critical) = low Pain relief speed (important) = low Functional outcomes (important) = low Sedation (important) = very low others omitted for no or indeterminate data]
Justification	The quality of the RCT evidence concerning the use of one of the analgesics studied over others was mixed – high for some comparisons and moderate, low, or very low for other comparisons. Across the many trials and comparisons, the GDG felt that there was no obviously-best treatment for maintenance of pain relief. The choice of opioid therefore largely depends on factors such as clinical assessment, cost, and patient preference. The GDG felt that a strong recommendation was warranted due to the strength of informed medical consensus on the administration of appropriate-strength analgesics to patients who need them. To suggest uncertainty in this regard risks undermining the strong case that low-resource settings would often achieve better coverage of adequate services by choosing cheaper options instead of the more expensive options frequently sold to them. It could also risk exacerbating widespread misconceptions on whether to use strong opioid analgesics or not. Furthermore, the GDG felt strongly that a range of weak and strong analgesic medications should be available to adult, adolescent, and older persons with cancer pain since there is variation in individuals' responses to specific analgesic medications, and wanted to be clear with a strong recommendation that having only a small selection was inadequate for appropriate treatment of mild, moderate, and severe pain. The GDG also saw this question as an opportunity to clarify that patients should be started on an analgesic that is appropriate to their level of pain, which was not clear from the 1996 guidelines which led to a common belief that patients should be started only on the first step of the cancer pain analgesic ladder, i.e. a non-opioid +/- adjuvant. It was felt that a conditional recommendation would not be clear enough that this practice is harmful and should be amended.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	