Evidence-to-Decision table 1.1		
In adults (including older persons) and adolescents with pain related to active cancer, are there any differences between NSAIDs, paracetamol (acetaminophen), and opioids at the stage of initiation of pain management in order to achieve rapid, effective and safe pain control?		
POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	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.[8] **<u>Current recommendations</u>** The current recommendations rely on the 1996 WHO Guidelines on Cancer Pain Relief, which employs the three step analgesic ladder, which recommends 'sequential use of drugs': first a non-opioid with or without an adjuvant; then if pain is not relieved, 'an opioid for mild to moderate pain should be added'; if this combination 'fails to relieve the pain, an opioid for moderate to severe pain should be substituted'. The GDG in 2017 were keen to note that this sequential recommendation was misleading as it implied that pain relief should start with non-opioids and ramp up to strong opioids, when in fact patients may enter at any point of the analgesic ladder. 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
INTERVENTION:	Analgesics (NSAIDS, paracetamol, opioids)	
COMPARISON:	Other analgesics	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Respiratory depression (adverse event) • Confusion (adverse event)	
STRATIFICATIONS:	• Age (adults, elderly, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		of ASA per day, maximum 6g paracetamol per day, maximum 3g ibuprofen per day, maximum 200mg indomethacin per day. The 1996 recommendations split opioid analgesics into those used for mild to moderate pain and those used for moderate to severe pain. It recommends opioid analgesics be given by mouth if possible. It notes that there is no standard recommended dose because responses of patients vary, and it recommends that dose takes into account tolerance and the development of physical dependence, as well as that lower starting doses be used in older persons. 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. 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 initiation of pain management. The recommended 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 specific starting 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. • 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. The GDG identified the initiation of pain management as a time point of interest. Given the variety of views on the topic outside of the GDG, they decided that evidence should be collected for all relevant medications, i.e. paracetamol, NSAIDs, and opioid analgesics.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** Yes	**Research evidence:** 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]. Up to date guidance is needed in order to overcome attitude and knowledge barriers to the delivery of adequate pain management[9]. **Additional considerations:** None.

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	**FIve randomized controlled trials** compared analgesics used at pain management initiation. All but one trial (that did not report data) included patients with multiple cancer types. All trials were conducted in adults or elderly adults, two of which were restricted to older persons. Six trials compared different opioids, one evaluated the addition of paracetamol, and one compared a NSAID to combination opioid and NSAID. **BENEFITS and HARMS** • Based on **one trial,** we are uncertain whether **high-potency opioid** or **low-potency opioid** better **relieve pain** as the strength of the evidence has been assessed a **very low** (RR 1.80; 95% CI 1.42, 2.29)**.** Based on **one trial,** we are uncertain whether **high-potency opioid + NSAID** or **NSAID alone** better **relieve pain** as the strength of the evidence has been assessed a **very low** (RR 1.36; 95% CI 0.98, 1.87)**.** • Based on **one trial,** we are uncertain whether **high-potency opioid or low-potency opioid reduce pain** more as the strength of the evidence has been assessed a **very low** (Net difference = -13; 95% CI -87, 60 on a 0-100 [worst] scale)**.** • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **respiratory depression.** • **Three trials** reported on confusion. The three trials provided **moderate strength of evidence of similar rates of confusion between morphine controlled release and oxycodone controlled release** (RR = 0.85; 95% CI 0.50, 1.44**).** **One trial** had **low strength of evidence of no differences among buprenorphine or fentanyl also compared to morphine controlled release and oxycodone controlled release.** **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** We are uncertain about relative pain relief effects of different classes of analgesics. Morphine controlled release and oxycodone controlled release probably result in similar rates of confusion. Buprenorphine and fentanyl may result in similar rates of confusion, also compared to morphine controlled release and oxycodone controlled release. **<u>Additional considerations</u>**

		The GDG were keen to note that this conclusion of uncertainty with regards to the balance of desirable vs undesirable effects for the studied analgesics does not indicate uncertainty about whether to use analgesics or not – the uncertainty pertains to difference *between* different medications, not to their use absolutely.
ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability yes Minor variability Uncertain **Is the option acceptable to key stakeholders?** Yes No Uncertain yes	**<u>Research Evidence:</u>** There is quite a lot of variability across countries, cultures, clinicians, families, and patients with regard to values on the use of opioid medications[10]. 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 took into account the often contradictory views of overall patient preference for strong analgesics, the views of their families, and variation in patient preferences with age. They also noted variability across populations with regard to individual side effects. They concluded that, with regard to different analgesics at the stage of initiation of pain management, there was major variation in how much people value the options.

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

	Would the option improve equity in health? Yes No Uncertai Yes ☐ ☐	**Research evidence** None presented. **Additional considerations** 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. The GDG also bore in mind the risk of unintended consequences. They noted that balanced regulations of these strong opioid medications, 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:** Previous guidelines recommended 'sequential use of drugs': first a non-opioid with or without an adjuvant; then if pain is not relieved, 'an opioid for mild to moderate pain should be added'; if this combination 'fails to relieve the pain, an opioid for moderate to severe pain should be substituted'. **New (draft) recommendation:** In adults (including the older person) and adolescents with pain related to active cancer, NSAIDs, paracetamol, and opioids (alone or in combination) should be used at the stage of initiation of pain management depending on clinical assessment and pain severity in order to achieve rapid, effective and safe pain control.
Strength of Recommendation	**Strong**
Quality of Evidence	➢ **Low** [Pain (critical) = very low Confusion = moderate (morphine vs. oxycodone CR) others omitted for no data]
Justification	The quality of the RCT evidence concerning the selection of a particular type of analgesic over others was low. The GDG were concerned that limiting a recommendation on this basis to a conditional recommendation would belie the strength of informed medical consensus on the administration of appropriate-strength analgesics to patients who need them, and would thus risk exacerbating widespread misconceptions in this area and concomitant lack of access and availability to many of these medications. 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.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	