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Is there an Ideal Opioid for Cancer Pain?

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Introduction

Opioids still the mainstay drugs regarding cancer pain management. Nowadays they are prescribed by many disciplines involved in cancer treatment including oncologists, surgeons, pain physicians, palliative care physicians and even general practitioners. However, many of these care givers have misbelieves and low awareness about the proper use of opioids in cancer pain. This may be due to absence of continuous medical education, absence of updated guidelines and/or multiple controversies regarding these drugs. Many physicians dream and believe that it is important to have an ideal opioid fulfilling the following criteria:-

1. Available in different forms.
2. Can be combined safely and effectively with other drugs.
3. Has high bioavailabilty.
4. Can be used for moderate to severe pain.
5. Can be used effectively in different types of pain.
6. Has wide range of safety with minimal side effects.
7. Has easy and safe rotation criteria.
8. Metabolised to harmless end products.
9. Can be used safely in organ dyfunctions.
10. Has minimal drug-drug interactions.

Unfortunately, there is no single opioid fulfilling all these criteria. Therefore, it is not a matter of seeking an ideal opioids but it is a matter of ideal using of available ones to get the proposed goals regarding proper treatment of cancer pain. However, getting that level of experience necessitates adequate knowledge, extensive training and finally putting proper guidelines according to the available opioids in each organization. The following discussion will focus on some important controversies and updated scientific data of opioids that may help reader to gain some necessary knowledge to build up his own suitable guidelines. Of course the WHO analgesic ladder must be mentioned here as the first developed guidelines for chronic pain management. There is a strong debate now regarding its validity and usefulness in view of availability of many new synthetic opioids and adjuvents. This ladder ignore drug-drug interactions, management of breakthrough attacks and importence of side effects of different drugs. However, its advantages are many as it is good and safe for beginners, specify strength of opioids to severity of pain and it is helpful for progressive disease situations. Many modifications were proposed such as removal of its second step and adding a fourth step regarding methods to improve the quality of life but till now there is no final approval for these changes. Proper starting with the right opioid category according to pain strength, adding of appropriate adjuvents, continuous monitoring of analgesia and side effects and readiness to rotate opioids safely are the cornerstones for successful use of this ladder [1,2]. Meanwile, the broader concept is that it is a continuum rather than this simple pharmacological ladder must be applied for cancer pain. This comprises psychological, spiritual and interventional modalities beside drugs. There are many important myths regarding opioid therapy in chronic cancer pain among physicians which may hinders the application of best practice. Correction of these misbelieves through CME and workshops is mandatory for both beginners and old practitioners to ensure updated correction and declaration in view of continuous innovation of new forms and drugs. Discarding these processes will lead to serious mispractice and/or conducting these false believes from physicians to patients. Accoringly, patients and families may refuse treatment or modify doses and forms by themselves which may increase suffering and risks. Table 1 summarizes some of these misbelieves

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Table 1: Myths and corrective facts regarding chronic opioid therapy [3,4].

Myth: COT for chronic pain is supported by strong evidence	Fact: Evidence of long-term efficacy for chronic non-cancer pain (≥16 weeks) islimited and of low quality. Opioids are effective for short-term pain management. But, for many patients with chronic pain, analgesic efficacy is not maintainedover long time periods.
Myth: Physical dependence only happens with high doses over long periods of time.	**Fact:** With daily opioid use, physical dependence and tolerance can develop in days or weeks
Myth: Patients who develop physical dependence on opioids can easily be tapered off.	**FACT:** Successfully tapering chronic pain patients from opioids can be difficult – even for patients who are motivated to discontinue opioid use
Myth: Addiction is rare in patients receiving medically prescribed COT.	**Fact:** Estimates vary. Between 4% and 26% of patients receiving COT have an opioidbuse disorder. Among patients without an opioid use disorder, more than one in ten misuse opioids by: intentional over-sedation; concurrently using alcohol for pain relief; hoarding medications; increasing dose on their own; and borrowing opioidsfrom friends.
Myth: Prescribing high-dose Extended-release opioid therapy (≥120 mg morphine equivalents/ day) is supported by strong evidence that benefit soutweigh risks.	**Fact:** Extended-release opioids have **not** been proven to be safer or more effective than short-acting opioids for managing chronic pain.
Myth: Opioid overdoses only occur among drug abusers and patients who attempt suicide.	**Fact:** Patients using prescription opioids are at risk of unintentional overdose and death. This risk increases with dose and when opioids are combined with other CNS depressants like benzodiazepines and alcohol.
Myth: Dose escalation is the best response when patients experience decreased pain control.	**Fact:** When treating chronic pain, dose escalation has **not** been proven to reduce pain or increase function, but it can increase risks??????/

Table 2: Strength of recommendations regarding chronic opioid therapy [5].

-Once stable pain control is achieved with immediate release morphine, a controlled release preparation should be used	-Analgesia for continuous pain should be given around the clock not on an as-required basis. -The World Health Organization ladder is useful for determining the initial opioid potency.	-The oral route is preferred and should be used where possible -When initiating morphine, start with an immediate-release preparation at 5–10 mg every 4 h
Patients with neuropathic pain should have a trial of an adjuvents	-All patients with moderate to severe pain should receive a strong opioid like morphine.	-Every patient should have access to rescue doses of analgesia for breakthrough pain
-Spinal opioids are effective in the management of cancer pain	-Patients receiving regular opioids must have access to regular prophylactic aperients. -The subcutaneous route is preferred for patients needing parenteral opioids. -Alternative opioids can be tried in patients with opioid-sensitive pain who are unable to tolerate morphine side effects. -Transdermal fentanyl is a suitable alternative to morphine for patients with stable dose requirements. -Psychological dependence/addiction is unlikely to occur in these patients	-Opioid toxicity should be managed by reducing the dose, ensuring adequate hydration and hydration and treatment of confusion/agitation with a major tranquillizer -The oral : parenteral ratio of morphine is 1:2 or 1:3

Table 3: Dose modifications of different opioids in liver and kidney dysfunctions.

OPIOID	DOSE IN RENAL DYSF UNCTION	DOSE IN LIVER DYSFUNCTION
MORPHINE	REDUCE INITIAL DOSE BY 50% IfcRCI LESS THAN 50ml/min,75% IF IT IS LESS THAN10ml/min	INCREASE DOSING INTERVAL TWICE
HYDROMORPHONE	AS MORPHINE	DOSE REDUCTION BY 50%
OXYCODONE	AS MORPHINE	DOSE REDUCTION BY 50-66%
METHADONE	APPEARS SAFE BUT IT NEEDS EXPERIENCE	NOT RECOMMENDED
FENTANYL	REDUSE DOSE BY 25% FOR CrCI LESS THAN 50 ml/min,50% IF IT IS LESS THAN 10%	APPEARS SAFE BUT MONITOR FREQUENTLY

and the facts that correct them while Table 2 summarizes the latest strength of recommendations regarding chronic opioid therapy.

One of the most challenging situation is how to use opioids in cases of renal and hepatic impairements which are very common problems faced during cancer journey. Unexperienced care givers may stop medications or use in either toxic or very low ineffective doses. Again there is no ideal opioid which can be used in such problems but the meticulous use of available ones according to recognized updated guidelines as illustrated in Table 3 [6-8].

In conclusion, we have no ideal opioid that ensure maximum efficacy and safety. Instead opioid regimen must be tailored to each patient according to his type and severity of pain, associated co-morbidities and safety use of available drugs. CME, training, awareness campaigns and following updated guidelines are mandatory to optimize therapy. Lastly, the following questions and answer clarify which controversies are resolved, which unresolved and which ones still need more research.

- Is cancer pain relief safe? Resolved: safe
- Is morphine the best strong opioid? Unresolved
- How is morphine metabolised? Partly resolved: hepatic; role of M3G.
- M6G (?); pharmacogenetics (?)
- What is the best route of administration? Unresolved
- What is the correct oral: parenteral ratio? Partly resolved
- Is the development of tolerance a problem? Resolved: no
- Is there a risk of addiction? Resolved: no
- Is cancer pain relief a form of euthanasia? Resolved: no
- Is the WHO ladder obsolete? Unresolved

- Is there a role for opioids in neuropathic pain? Unresolved
- What is the role for opioid roation in pain management? Unresolved
- What is current status of evidence-based cancer pain management? Unresolved

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