Considerations For Opioid Prescribing in Palliative Care

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About Palliative.info

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Palliative.info offers an organized, up-to-date collection of links to palliative care resources on the internet, as well as locally developed palliative care material.

... more info ...

What is Palliative Care? (a personal definition)
Palliative Care is an approach to care which focuses on comfort and quality of life for those affected by life-limiting/life-threatening illness. Its goal is much more than comfort in dying; palliative care is about living, through meticulous attention to control of pain and other symptoms, supporting emotional, spiritual, and cultural needs, and maximizing functional status. The spectrum of investigations and interventions consistent with a palliative approach is guided by goals of patient and family and by accepted standards of health care, rather than being boundaried by preconceptions of what is or is not "palliative".

See also the World Health Organization’s definition

Links Grouped by Topic:

- Aboriginal / Indigenous Peoples
- Advance Directives (Health Care Directives)
- Advocacy, Govt Policy
- Assessment/Evaluation Tools
- Programs
- Psychosocial Professional
- Quality of Life
- Research Sites Related to Palliative Care
- Specific Diseases/Populations
- Spiritual / Faith-Based
- Standards and Norms

Teaching Material

- Manitoba Resources - Lectures/Presentations/Handouts
- Ian Anderson Modules
- StopPain.org: Topics in Pain Management - A Slide Compendium

Local (Winnipeg) Documents
## Events / Conferences

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<td>6th Annual Nurse Practitioner Association of Manitoba Conference - Nov. 7, 2014</td>
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<td>1. Considerations For Opioid Prescribing in Palliative Care</td>
<td>Mike Harlos</td>
<td>PowerPoint® pdf version</td>
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<tr>
<td>WRHA Palliative Care Program Noon Rounds Nov. 5, 2014</td>
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<td>1. Intranasal Medications in Palliative Care</td>
<td>Mike Harlos</td>
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## Resident Teaching Material

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<td>Communication and Decision Making in Palliative Care</td>
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<td>Pediatrics: Academic Half Days</td>
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<td>PowerPoint®</td>
<td>Dr. Chris Holt, Dr. Mike Harlos, Erin Shepherd</td>
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## Topic-Specific

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<tr>
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<th>Forum</th>
<th>File Format*</th>
<th>Topic (Click On Title To View Or Download)</th>
<th>Author**</th>
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<tr>
<td></td>
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<td></td>
<td>General Palliative Care Topics</td>
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</table>
The presenter has no conflict of interest to disclose
Objectives

- to review the role of opioids in palliative care
- to review considerations related to opioid prescribing in managing pain and dyspnea in palliative care
- to consider some of the ethical concerns sometimes associated with opioid prescribing in patients at end of life
Opioids

- **Opiates**: a group of naturally occurring compounds derived from the juice of the poppy *Papaver somniferum*
  - morphine is the classic opiate in clinical use

- **Opioids**: refers to these, as well as semisynthetic (e.g. hydromorphone) and synthetic (fentanyl, methadone) drugs that act on opioid receptors (\textit{mu}, delta, kappa)

- primary uses in palliative care are management of pain and dyspnea
Strong Opioids

• most commonly use morphine, hydromorphone, fentanyl, methadone, oxycodone

• codeine tends not to be used
  – pro-drug of morphine – might as well use low-dose morphine
  – high variability in metabolizing to morphine

• usually reasonable to start with morphine, unless significant renal impairment
Approach To Pain Control in Palliative Care

1. Thorough assessment
   - History – including detailed description of pain; psychosocial, spiritual, & cultural context; concerns about what the pain means; medication history
   - Physical Examination – don’t forget neuro exam

2. Pause here - discuss with patient/family the goals of care, hopes, expectations, anticipated course of illness. This will influence consideration of investigations and interventions

3. Investigations – X-Ray, CT, MRI, etc - *if they will affect approach to care*

4. Treatments – pharmacological and non-pharmacological; interventional analgesia (e.g. spinal); RadTx

5. Ongoing reassessment and review of options, goals, expectations, etc.
Considerations When Starting An Opioid

• are opioids appropriate for the symptom, or might other measures be added? (adjuvant analgesics, RadTx)
  - not all pain syndromes are expected to respond fully to opioids – specifically neuropathic pain

• should you start with *prn* dosing or regular dosing?
  - depends on the context
  - *prn* reasonable for occasional pain, or when the pattern is unknown or erratic and baseline opioid requirements need to be determined
  - regular dosing should be provided for pain that is consistent, progressive and not expected to resolve
  - you end up using more opioids chasing pain than remaining ahead of it
Considerations When Starting An Opioid

• what route(s) of administration are available, and is that expected to change?
  – e.g. recurrent bowel obstruction, progressive dysphagia

• are there circumstances that warrant a conservative approach?
  – pediatrics
  – frail elderly
  – starting opioids for dyspnea in an end-stage COPD patient (unless severe distress compels an aggressive approach, in which case you remain with patient until comfortable)
“Start Low, Go Slow”

• If you start cautiously with an anticipated ineffective dose, be prepared to titrate up quickly

• “prepared” means attentive, proactive, vigilant, available (i.e. don’t assume things are fine if nobody calls you)

• “first-dose survival test”

• Reassess early (perhaps later that day even), and consider increasing to a more “usual” dose
Some Overarching Principles

- Doses proportionate to the degree of distress are safe.
- Anticipate and preempt predictable ("incident") pain.
- Dose increases 10% - 100%, depending on the context; usually should achieve steady state (5 half-lives) before increasing dose.
- IV, subcut administration bypass first-pass metabolism in the liver, and doses usually ½ the po dose.
- Short-acting opioids (typically morphine, hydromorphone) should be used during dose titration and when pain is unstable.
Switching Between Short-Acting And Long-Acting Preparations Of The Same Opioid

• usually simply add up the total daily opioid dose, and divide by the # doses per 24 hrs

• e.g.: MS-Contin® 100 mg tid
  = 300 mg/day
  = 50 mg q4h of short-acting prep

• e.g.: hydromorphone 8 mg q4h
  = 48 mg/day
  = 16 mg tid of long-acting hydromorphone prep
# Considerations In Opioid Selection

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Routes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>po, SL*, subcut, IV, IM, pr</td>
<td>• metabolite (M3G, M6G) accumulation in renal insuff</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>po, SL*, subcut, IV, IM, pr, intranasal (IN)*</td>
<td>• metabolite accumulation (H3G) in renal insuff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ? better tolerated in elderly than morphine (no literature)</td>
</tr>
<tr>
<td>oxycodone</td>
<td>po</td>
<td>• parent drug may accumulate in renal insuff – need to watch</td>
</tr>
<tr>
<td>fentanyl</td>
<td>IV, subcut, SL*, IN*, transdermal</td>
<td>• no active metabolites; a preferred choice in renal insuff</td>
</tr>
<tr>
<td>methadone</td>
<td>po, SL*, IV**</td>
<td>• requires exemption from Health Canada / CPSM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• no active metabolites; a preferred choice in renal insuff</td>
</tr>
</tbody>
</table>

* off-label use  ** must be obtained from outside Canada through Health Canada
Determining The Correct Opioid Dose

Somewhere in here

Not Enough  Too Much

i.e. the opioids are titrated proportionately to achieve the desired effect
# Sample Adult Doses

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Usual Adult Starting Doses</th>
<th>Potential Starting Doses In Frail Elderly or Advanced Resp Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>po 5 – 10 mg q4h</td>
<td>po 1 – 2 mg q6h</td>
</tr>
<tr>
<td></td>
<td>IV/SC 2.5 – 5 mg q4h</td>
<td>IV/SC 0.5 – 1 mg q6h</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>po 1 mg q4h</td>
<td>po 0.25 – 0.5 mg q6h</td>
</tr>
<tr>
<td></td>
<td>IV/SC 0.5 mg q4h</td>
<td>IV/SC 0.125 – 0.25 mg q6h</td>
</tr>
<tr>
<td>oxycodone</td>
<td>po 5 mg q6h</td>
<td>It would be extremely unusual to start a frail elderly or resp patient on oxycodone rather than morphine or hydromorphone</td>
</tr>
</tbody>
</table>
Opioid Conversions

- conversions are usually based on single-dose studies in opioid-naïve patients (not tolerant to opioids)
- with ongoing exposure to an opioid, tolerance develops
- when opioids are switched, this tolerance is not fully crossed over = Incomplete Cross-Tolerance
- cannot use conversion tables to determine the dose of an alternative opioid without considering the clinical context
- might consider decreasing the calculated dose by 50%, but even that depends on the situation
Considerations In Switching Opioids

- If you are switching because of adverse effects such as nausea, and the baseline pain control is:
  - *poor*: don’t usually decrease the calculated dose – the patient needs an opioid increase
  - *good*: likely should decrease the calculated dose by 50% due to incomplete cross-tolerance

- When switching opioids in any high dose situation, be very careful about the potential risk caused by incomplete cross-tolerance

- in suspected opioid-induced neurotoxicity with opioid-induced hyperalgesia, don’t even try to calculate an alternative opioid.
  - discontinue the offending opioid, and use *prn* dosing of a suitable alternative to determine opioid needs
<table>
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<tr>
<th>Relative Analgesic Ratios For Opioid Switching</th>
<th>Relative analgesic ratio</th>
<th>Strength of the recommendation for use</th>
</tr>
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<tbody>
<tr>
<td>Oral morphine to oral oxycodone</td>
<td>1:1.5</td>
<td>Strong</td>
</tr>
<tr>
<td>Oral oxycodone to oral hydromorphone</td>
<td>1:4</td>
<td>Strong</td>
</tr>
<tr>
<td>Oral morphine to oral hydromorphone</td>
<td>1:5</td>
<td>Weak</td>
</tr>
<tr>
<td>Oral morphine to TD buprenorphine*</td>
<td>75:1</td>
<td>Weak</td>
</tr>
<tr>
<td>Oral morphine to TD fentanyl†</td>
<td>100:1</td>
<td>Strong</td>
</tr>
</tbody>
</table>

TD=transdermal. *Example: 60 mg oral morphine to 35 μg/h TD buprenorphine (equivalent to 0.8 mg per 24 h). †Example: 60 mg oral morphine to 25 μg/h TD fentanyl (equivalent to 0.6 mg per 24 h).

Basic Conversions – Starting Points For Consideration

<table>
<thead>
<tr>
<th>Drug Conversion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine:hydromorphone</td>
<td>hydromorphone is about 5 times more potent than morphine</td>
</tr>
<tr>
<td>5 mg morphine = 1 mg hydromorphone</td>
<td></td>
</tr>
<tr>
<td>morphine:oxycodone</td>
<td>oxycodone is about 1.5 times more potent than morphine</td>
</tr>
<tr>
<td>1.5 mg morphine = 1 mg oxycodone</td>
<td></td>
</tr>
<tr>
<td>Methadone to anything</td>
<td>Context dependent</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>Use drug monograph</td>
</tr>
</tbody>
</table>
Conversion Examples

• 65 yo man with metastatic lung CA on morphine 30 mg q4h, good pain control, nauseated with morphine, switching to hydromorphone
  – 30 mg morphine ≈ 6 mg hydromorphone
  – reduce due to incomplete cross-tolerance
  – 3 or 4 mg hydromorphone q4h would be a reasonable initial conversion

• same patient, but the context is one of suboptimal pain control
  – reasonable to start with hydromorphone 6 mg q4h
Case Report

Overdose Deaths Demand a New Paradigm for Opioid Rotation

Lynn R. Webster, MD,* and Perry G. Fine, MD†

1. ↓current dose 10 - 30% while beginning new opioid at opioid-naïve dose or at the lowest available dose for the formulation.
2. Slowly ↓original total daily opioid dose by about 10 - 25% per week while ↑new daily opioid dose by about 10 - 20% based on clinical need and safety. In most instances, the complete switch can occur within 3 - 4 weeks.
3. Provide sufficient immediate-release opioid throughout the rotation to prevent withdrawal and/or increased pain if the dosing changes prove insufficient.
Breakthrough Doses

- breakthrough doses are usually 10-20% of total daily dose, or equal to the q4h dose
- the correct dose is the one that works – this may vary for an individual patient, and might be substantially different between patients
- *prn* interval for breakthroughs should reflect pharmacology – i.e. when is it reasonable to repeat? (enteral 1 hr; subcut 30 min; IV 10-15 min; transmucosal 10-15 min)
- if you want to limit the # breakthrough doses due to safety concerns, do so by limiting the # doses over a period, but keep the reasonable interval
Stacking Doses

- **Time**
- **Opioid Level**
Breakthrough Dose Examples

• Patient on 100 mg tid MS-Contin® = 300 mg/day
  Breakthrough dose should be short-acting morphine 30 mg po q1h prn

• Patient on 8 mg hydromorphone q4h subcut
  Breakthrough dose should be 8 mg subcut q30 min prn
  (sometimes we end up writing q1h prn, as sometimes the facility is not comfortable with a short interval)
Transdermal Fentanyl

• not for use in opioid-naïve patients
• not for use in unstable pain
• particularly useful when pain control is stable in an opioid-tolerant patient and:
  – oral route is compromised, or vulnerable (e.g. recurrent bowel obstruction, head and neck CA, ALS, etc)
  – simplifying a medication regimen in a non-compliant or confused patient (may need to put “out of sight” – e.g. intrascapular)
  – simplify a medication regimen for other reasons – traveling, facilitating medication storage or diversion issues, less complex for family caregivers
Transdermal Fentanyl

- approx 100 x more potent than morphine – i.e.
  50 mcg fentanyl (= 0.05 mg fentanyl) ≈ 0.05 x 100
  = 5 mg morphine

- titrate no more often than q3d (each patch change)

- “the gift that keeps giving” – it takes approx 17 hrs for
  serum levels to reduce by 50% once the patch is
  removed

- patients may put it where it hurts – same with heating
  pads and hot water bottles
Changes In Plasma Fentanyl Concentration With Heat Application
Clinical note

Transdermal fentanyl in cachectic cancer patients

Tarja Heiskanen\textsuperscript{a,*}, Sorjo Mätzke\textsuperscript{b}, Soile Haakana\textsuperscript{a}, Merja Gergov\textsuperscript{c}, Erkki Vuori\textsuperscript{c}, Eija Kalso\textsuperscript{a,\dagger}

\textsuperscript{a}Pain Clinic, Department of Anesthesiology and Intensive Care Medicine, Helsinki University Central Hospital, P.O. Box 140, 00029 HUS Helsinki, Finland

\textsuperscript{b}Department of Clinical Physiology, Jorvi Hospital, Espoo, Finland

\textsuperscript{c}Department of Forensic Medicine, University of Helsinki, Helsinki, Finland

\textsuperscript{\dagger}Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland

- plasma fentanyl concentrations significantly lower in cachectic patients
- impaired transdermal fentanyl absorption in patients with cancer-related cachexia
- seems to be an issue of absorption
## Converting To Transdermal Fentanyl

As Per Duragesic® Monograph

**Dose Conversion Guidelines are Unidirectional and for Chronic Use.**

Use this table to convert patients from the Current Analgesic ONLY to DURAGESIC® MAT.

Do NOT use this table to convert patients from DURAGESIC® MAT to other opioids; doing so may result in overdose and toxicity.

<table>
<thead>
<tr>
<th>Current Analgesic</th>
<th>Daily Dosage (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine</td>
<td>60-134 135-179 180-224 225-269 270-314 315-359 360-404</td>
</tr>
<tr>
<td>IM/TV morphine (based on a 1:3 IM:PO ratio)</td>
<td>20-44 45-60 61-75 76-90 NA² NA² NA²</td>
</tr>
<tr>
<td>Oral codeine</td>
<td>150-447 448-597 598-747 748-897 898-1047 1048-1197 1198-1347</td>
</tr>
<tr>
<td>IV hydromorphone³</td>
<td>4.0-8.4 8.5-11.4 11.5-14.4 14.5-16.5 16.6-19.5 19.6-22.5 22.6-25.5</td>
</tr>
<tr>
<td><strong>DURAGESIC® MAT DOSE</strong></td>
<td>25 mcg/h 37 mcg/h 50 mcg/h 62 mcg/h 75 mcg/h 87 mcg/h 100 mcg/h</td>
</tr>
</tbody>
</table>
# Opioid Breakthrough Doses For Patients Receiving Transdermal Fentanyl

<table>
<thead>
<tr>
<th>Oral Morphine (MG q 1h PRN)</th>
<th>Transdermal Fentanyl (mcg / hr)</th>
<th>Oral Hydromorphone (mg q 1h PRN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>2</td>
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<td>110</td>
<td>275</td>
<td>22</td>
</tr>
<tr>
<td>120</td>
<td>300</td>
<td>24</td>
</tr>
</tbody>
</table>
Opioid Side Effects

- **Constipation** – need proactive laxative use
- **Nausea/vomiting** – consider treating with dopamine antagonists and/or prokinetics (metoclopramide, domperidone, prochlorperazine [Stemetil], haloperidol)
- **Urinary retention**
- **Itch/rash** – worse in children; may need low-dose naloxone infusion. May try antihistamines, however not great success
- **Dry mouth**
- **Respiratory depression** – uncommon when titrated in proportion to symptom
- **Drug interactions** – additive sedation, enzyme induction or inhibition
- **Neurotoxicity (OIN):** delirium, myoclonus, seizures
Opioid-Induced Constipation

• assume that someone prescribed opioids will become constipated
• “The hand that writes the opioid prescription should write the laxative prescription” (Dame Cicely Saunders)
• Librach SL et al; J Pain Symptom Manage. 2010;40(5):761-73) – Consensus recommendations:
  1. Osmotic laxatives, lactulose, and PEG are supported by Grade A evidence and are recommended in the appropriate patient.
  2. Use of docusates is not recommended.
  3. Use of mineral oil is not recommended.
  4. Stimulants such as senna base laxatives and bisacodyl can be used despite the insufficient evidence of efficacy.
  5. If constipation persists, an enema or suppository may be needed.
Spectrum of Opioid-Induced Neurotoxicity

- Opioid tolerance
- Mild myoclonus (eg. with sleeping)
- Severe myoclonus
- Seizures, Death

Opioids Increased → Misinterpreted as Pain

Delirium → Agitation

Hyperalgesia → Misinterpreted as Disease-Related Pain
“Allergic” To Morphine

- true allergy to an opioid is very uncommon
- adverse effects such as delirium, pruritus often labeled as allergy
- morphine and to some degree hydromorphone can cause histamine release from mast cells, with urticaria and pruritus – not an immune-mediated phenomenon, not an allergy
- fentanyl tends not to cause histamine release
- if pain is mild to moderate, might consider tramadol
- if a strong opioid is needed, it would be reasonable to try an opioid from a different class
Phenanthrenes
- morphine
- hydromorphone
- oxycodone

Phenylpiperidines
- fentanyl
- sufentanil

Diphenylheptanes
- methadone
# Opioids And Dyspnea

<table>
<thead>
<tr>
<th>Areas With Initial Evidence From Rigorously Designed Studies Focusing on Regularly Administered, Low-Dose Opioids to Treat Breathlessness</th>
<th>Areas in Which Further Rigorously Designed Studies Are Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Efficacy&lt;sup&gt;17–19&lt;/sup&gt;</td>
<td>1. Is there a class effect from opioids? Do mu-opioid agonists deliver the most benefit?</td>
</tr>
<tr>
<td>2. Effective routes of administration (oral, parenteral)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2. Can we define particular subgroups of people for whom opioids are more beneficial?&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>3. Safety and tolerability&lt;sup&gt;20&lt;/sup&gt;</td>
<td>3. What is the true role of opioids in the relief of breathlessness in clinical practice?</td>
</tr>
<tr>
<td>4. Minimal change in efficacy required for patient-defined benefit (minimal clinically important difference)&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>4. What is the role of other routes of administration such as intranasal, buccal, transdermal, or nebulized?</td>
</tr>
<tr>
<td>5. Definition of a central mechanism of action&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>5. What other opioid mechanisms help to ameliorate breathlessness?</td>
</tr>
<tr>
<td>6. Definition of a central mechanism of action&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>6. Are there agents that synergistically enhance the efficacy of opioids?</td>
</tr>
<tr>
<td>7. Definition of a central mechanism of action&lt;sup&gt;23,24&lt;/sup&gt;</td>
<td>7. What are the barriers and facilitators to opioid prescribing in breathlessness?</td>
</tr>
</tbody>
</table>

Medical Observations

Why Opioids and Sedatives May Prolong Life Rather Than Hasten Death After Ventilator Withdrawal in Critically Ill Patients

Jan Bakker, MD, PhD, Tim C. Jansen, MD, Alex Lima, MD, and Erwin J. O. Kompanje, MD, PhD

- may reduce overall oxygen demand
- “The administration of sedatives (midazolam and morphine) has been associated with decreases in oxygen demand and the attenuation of the cardiopulmonary response associated with increased work of breathing”
- see also: Endoh H et al; Effects of naloxone and morphine on acute hypoxic survival in mice. Crit Care Med; 1999;27(9):1929-33
  - significantly lower oxygen consumption and improved survival in morphine treated rats subjected to acute hypoxic hypoxia
Common Concerns About Aggressive Use of Opioids at End-Of-Life

• How do you know that the aggressive use of opioids for dyspnea doesn't actually bring about or speed up the patient's death?

• "I gave the last dose of morphine and he died a few minutes later... did the medication cause the death?"
1. **Literature:** the literature supports that opioids administered in doses proportionate to the degree of distress do not hasten death and may in fact delay death

2. **Clinical context:** breathing patterns usually seen in progression towards dying (clusters with apnea, irreg. pattern) vs. opioid effects (progressive slowing, regular breathing; pinpoint pupils)

3. **Medication history:** usually “the last dose” is the same as those given throughout recent hours/days, and was well tolerated
TOLERANCE

PHYSICAL DEPENDENCE

≠

PSYCHOLOGICAL DEPENDENCE / ADDICTION
TOLERANCE

A *normal* physiological phenomenon in which *increasing doses are required to produce the same effect*

*Inturrisi C, Hanks G. Oxford Textbook of Palliative Medicine* 1993: Chapter 4.2.3
PHYSICAL DEPENDENCE

A *normal* physiological phenomenon in which a *withdrawal syndrome occurs when an opioid is abruptly discontinued* or an *opioid antagonist is administered*

*Inturrisi C, Hanks G. Oxford Textbook of Palliative Medicine 1993: Chapter 4.2.3*
PSYCHOLOGICAL DEPENDENCE and ADDICTION

A pattern of drug use characterized by a continued craving for an opioid which is manifest as compulsive drug-seeking behaviour leading to an overwhelming involvement in the use and procurement of the drug.

Inturrisi C, Hanks G. *Oxford Textbook of Palliative Medicine* 1993: Chapter 4.2.3