



Opioids for Pain in the Elderly

Twenty-seven percent of the elderly population living at home and 38% of the long-term care elderly population report chronic pain, compared to 16% of those aged 18 to 64.¹ In elderly patients with persistent pain, acetaminophen is considered first line pharmacotherapy; however, unlike the WHO pain ladder for treatment of cancer pain,² non-steroidal anti-inflammatories are discouraged except for select patients.³ Because of the limited alternatives, opioids may need to be considered sooner in the course of chronic pain in an elderly patient.

Drug Metabolism Changes Affected by Aging:

Inevitable changes in metabolism that occur with aging can modify medication effect and increase the risk for adverse events. Within the elderly adult population, it becomes more difficult to attain optimal serum concentrations of medications and, similarly, it can become harder to clear medications from the system.^{3,4} Liver metabolism may slow, resulting in longer half-lives of medications. Similarly, glomerular filtration rate decreases with age, causing reduced excretion and prolonged effects of any active metabolites of the medication.^{3,4}

Opioid Use in Elderly Adults:

Evidence suggests that many elderly patients who might benefit from opioid therapy are not receiving it.^{3,5} As a class, opioids may be less likely to cause organ toxicity than NSAIDs.⁵ However, recent observational data challenges this assumption.⁶ More studies are needed to determine the relative safety of NSAIDs versus opioids for treatment of chronic pain in the elderly. In single-dose studies, opioids appear to cause less cognitive impairment than benzodiazepines.^{3,5} Very low rates of abuse and addiction have been associated with opioid use in clinics caring for elderly patients with well-defined pain conditions.⁵ However, elderly patients may be less likely to accept opioid analgesics because they may fear addiction, associate opioids (particularly morphine) with illness, and fear that complaining may lead to investigations or hospitalization.^{3,5} Also, some physicians are reluctant to prescribe opioids for elderly patients and this can further contribute to underutilization.⁵

The Canadian Guidelines for Safe and Effective Use of Opioids for Chronic Non Cancer Pain were published in April, 2010. According to these guidelines, opioid therapy for elderly patients may be safe over the long term, but can be dangerous when starting or increasing a dose.⁵ The following precautions are recommended: lower starting doses, slower titration, longer dosing intervals, more frequent monitoring, and discontinuing (by tapering) benzodiazepine use when possible.⁵ Evidence shows that chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200

mg/day of morphine or equivalent.⁵ Consideration of a higher dosage calls for reassessment of the pain and may lead to potential risk for misuse. Overall, a 30% or greater reduction in pain intensity is considered clinically significant.⁵

Risks of Opioid Use in Elderly Adults:

When it comes to risks of opioid use in the elderly the primary concerns are *overdose, oversedation and falls*.⁵ Pharmacokinetic factors that put the elderly at higher risk for opioid overdose than younger patients include lower serum binding, lower stroke volume (which acts to slow liver metabolism), as well as a greater sensitivity to the psychoactive and respiratory effects of opioids.⁵ Regarding the risk of oversedation, a high proportion of elderly patients on opioids are also on benzodiazepines and other psychotropic medications - the concomitant use of such medications can act to increase the risk of sedation.⁵

The Canadian Guidelines define patients at higher risk of opioid overdose as those with:⁵

- (i) renal or hepatic impairment as opioids are metabolized in the liver and excreted through the renal system
- (ii) chronic obstructive pulmonary disease (COPD) and sleep apnea due to the fact that tolerance to the respiratory depressant effects of opioids develops slowly thereby putting COPD patients at greater risk for respiratory depression with higher dose increases. Opioids may be a risk factor for central sleep apnea
- (iii) sleep disorders, as this may be a reflection of the effects of pain, or the sedating effects of opioids or concurrent depression
- (iv) cognitively impaired, patients with a psychiatric diagnosis or patients who live alone should avoid opioids, unless ongoing medication supervision can be arranged.

Reducing Opioid Related Risks in the Elderly Adult Population:

The Canadian Guidelines recommend the following strategies to decrease the potential for opioid-induced adverse effects in the elderly:⁵

- Educate the patient and caregiver to be able to recognize signs of overdose (i.e. slurred or drawling speech, emotional instability, mood changes, incoordination, nodding off during conversation or activity) so that the appropriate steps can be taken to minimize further harm.
- Avoid opioids in cognitively impaired patients living alone unless medication use can be supervised.
- Regular follow-up in the first 1-3 days is necessary to assess and deal with any dosing related issues.

A recently published cohort study suggests there may be different risks associated with the use of various opioids.⁷ The study reported an increase in all-cause mortality among patients who used codeine and oxycodone (versus hydrocodone) after one month and an increased risk of cardiovascular events after six months of codeine. On the other hand, tramadol was associated with a lower risk of fracture after one month. If these results are confirmed, adverse effect profiles of individual opioids will also be factors in the choice of appropriate opioid therapy for an elderly patient.

General Opioid Selection Recommendations for the Elderly:

The Canadian Guidelines recommend the following stepped approach to opioid selection based on the degree of pain:⁵

Degree of Pain	1st Line Choice	2nd Line Choice	3rd Line Choice
Mild to moderate	codeine* tramadol** buprenorphine patch***	morphine, oxycodone or hydromorphone	n/a
Severe	morphine, oxycodone, or hydromorphone	fentanyl	methadone

* the role for codeine in the elderly is often limited due to the extent of its constipating/GI effects

** cost / drug plan coverage may be an issue

*** transdermal buprenorphine is a fairly new product; cost/drug plan coverage may be an issue

Canadian Guidelines for General Opioid Prescribing for the Elderly:⁵

1. Start initial titration at no more than 50% of the suggested initial adult dose; lengthen the time interval between dose increases if necessary.
2. Among strong opioids, oxycodone and hydromorphone may be preferred over oral morphine for the elderly if constipation and sedation are an issue. Morphine should also be used with caution in patients with decreased renal function as the M-6 glucuronide metabolite of morphine accumulates and has been associated with adverse effects.
3. For chronic pain, controlled-release (CR) formulations offer compliance advantages although they are more expensive and there is no evidence they are any more effective than immediate-release (IR) formulations. For breakthrough pain or activity-related pain, IR formulations are necessary.
4. Morphine solutions are useful in some situations such as patients with swallowing problems, or patients requiring less than 5 mg morphine per tablet.
5. For elderly patients on benzodiazepines, try to taper the benzodiazepine dose to reduce the risk of falls and cognitive impairment. The combination of opioids and benzodiazepines increases the risk of sedation, overdose, falls and diminished function in all patients, especially as age advances.
6. Before prescribing an opioid, an environmental assessment for potential addiction/diversion risk should be conducted. The elderly may be a target for drug theft, etc. Proper storage and limited discussion surrounding the opioid is prudent.

Transdermal Opioid Patches:

Fentanyl: In a select group of elderly patients, transdermal fentanyl can be beneficial if used appropriately.⁵

Advantages:^{8,9}

- Patients who have swallowing difficulty or who prefer not to take oral medications
- Continuous analgesia for up to 72 hours

Disadvantages:^{3,8,9}

- Delayed onset of action, making it difficult to use in the patient with acute pain, and titration becomes longer and more challenging
- Highly protein-bound, which increases the risk of overdose in the frail patient (decreased plasma protein resulting in higher free fentanyl levels combined with the reduced ability to metabolize fentanyl)

- As body temperature increases, the absorption of the drug can increase, and therefore may be problematic with febrile patients or those who use heating pads, etc.
- Once the patch is removed, the time to drug elimination is significantly longer (>24hours) in the elderly patient.
- **CONTRAINDICATED IN OPIOID-NAÏVE PATIENTS**

Canadian Guidelines for Fentanyl Transdermal Patch Use:⁵

1) **Ensure patients are fully opioid tolerant before they start therapy with fentanyl patches.** Obtain a complete history of opioid use within the last 2 weeks. Patches should only be used in patients who have received opioid therapy for at least 2 weeks in a total daily dose equivalent to fentanyl 25 µg/hour patch.^{4,7} In general, patients should be on at least the equivalent daily dose of 60 mg oral morphine for one week or longer before starting the patch.^{4,7} This dose should be scheduled rather than PRN (at least BID for CR formulations or QID for IR formulations).

2) **Patients should NOT be switched from codeine to fentanyl** regardless of the codeine dose, as some codeine users may have little or no opioid tolerance. Up to 10% of Caucasians lack the enzyme CYP450 2D6 that converts codeine to morphine; therefore when taking codeine they are exposed to little or no morphine.

3) The initial dose should be maintained for at least 6 days. Use extra caution with patients at higher risk for overdose, (i.e., elderly patients, concurrent use of benzodiazepines or other sedating drugs). It is appropriate to initiate these patients on a lower dose than the conversion tables recommend, including the use of the 12 µg/h dose by itself or in combination with another dose.

4) Advice for the patient / caregiver:

- Be alert for signs of overdose (see above) - if detected, remove the patch and seek medical attention.
- Apply as prescribed; do not apply more than one patch at a time or change more often than directed.
- Avoid heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing.
- Dispose of patches safely; a used patch contains a large amount of fentanyl and could be dangerous to others.

Why are such precautions necessary for fentanyl? It can cause significant cognitive impairment in non-tolerant opioid patients. As well, fentanyl has contributed to numerous overdose deaths.⁹⁻¹¹ For example, fentanyl was a contributing cause in 100 overdose deaths in Ontario between 2002 and 2004. In 54 of the deaths, fentanyl intoxication was the sole cause of death. Deaths occurred from both therapeutic and illicit use.^{5,9,10} Caution is advised with all fentanyl dosage forms.^{9,10,12,13}

Buprenorphine: A transdermal patch containing buprenorphine has recently been approved for use in Canada. In comparison to fentanyl, buprenorphine patches:

- Provide analgesia for up to one week; however they have a delayed onset of effect and limited titration range.¹⁴ Results are modest (NNT for 50% reduction in pain = 7-8 & NNH for adverse events = 6-9).¹⁵

- Can be used in opioid naïve patients (initiation doses higher than the 5µg/h patch should not be used in opioid naïve patients)^{14,15}
- Are an option when strong opioids are undesirable in chronic non-cancer pain¹⁵
- Have lower abuse potential¹⁵
- Have mild withdrawal symptoms¹⁵

In elderly patients, buprenorphine patches may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance; therefore they should be considered only for patients weighing $\geq 40\text{kg}$.^{11,12} Patients on high doses of morphine and/or strong opioids should NOT be switched to transdermal buprenorphine due to potential to precipitate opioid withdrawal.¹² For more information about buprenorphine patches, go to www.rxfiles.ca - BuTrans® Q&A.

Final Points for Consideration:

Opioids have been extensively studied in cancer pain, nonetheless it has been clearly demonstrated that opioids can improve pain and function in nonmalignant pain.^{3,5,16} It is also common to use opioids in combination with other drugs such as NSAIDs, anticonvulsants, and antidepressants to treat pain.^{3,16} In appropriately selected and monitored patients, opioid analgesics can be considered as part of a comprehensive strategy in the management of persistent cancer and non-cancer pain.^{3,5,16} In addition to determining the level of analgesia being produced, adverse events also need to be predicted and prevented in order to allow patients to be optimally managed. By selecting the appropriate combination of medications and non-pharmacologic interventions, clinicians can help manage their patients' pain and improve the quality of their lives at any age.

In summary, pharmacists should:

- Be prepared to discuss patient concerns regarding opioid use.
- Assess patients starting therapy on these medications and ensure appropriate use given patient parameters (i.e. opioid naïve?).
- Facilitate ongoing monitoring for adverse effects and pain control by the patient, the patient's caregiver and/or healthcare professional.
- Ensure that adverse effects associated with these medications are reported to Canada Vigilance.

References:

1. Ramage-Morin P. Chronic pain in Canadian seniors. Health Reports. Available at <http://www.statcan.gc.ca/pub/82-003-x/2008001/article/10514-eng.htm>. Accessed Dec. 2010.
2. WHO. WHO's pain ladder. Available at <http://who.int/cancer/palliative/painladder/en/>. Accessed Dec 2010.
3. American Geriatric Society Panel. Pharmacologic Management of Persistent Pain in Older Patients. JAGA. Available at http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf. Accessed Nov. 2010
4. Janora D, Jermyn R, Sajid A, Surve, D. Pharmacologic Management of Pain in Older Patients. Clinical Geriatrics. 2010;18:23-32. Available at <http://www.clinicalgeriatrics.com/articles/Pharmacologic-Management-Pain-Older-Patients>. Accessed Nov 2010.
5. National Opioid Use Guideline Group. Canadian Guidelines for Safe & Effective Use of Opioids for Chronic Non-Cancer Pain. Available at http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf. Accessed Nov 2010.
6. Solomon D, Rassen J, Glynn R et al. [The comparative safety of analgesics in older adults with arthritis](#). Arch Int Med 2010;170:1968-78.
7. Solomon D, Rassen J, Glynn R et al. [The comparative safety of opioids for nonmalignant pain in older adults](#). Arch Int Med 2010;170:1979-86.
8. e-CPS. Duragesic Monograph. Available at <https://www.e-therapeutics.ca/cps.showMonograph.action?simpleMonographId=m701838>. Accessed Dec 2010.

9. Canadian Pharmacists Letter. Safe Use of Fentanyl (Duragesic) Patches. Detail-Document; Canadian Pharmacist's Letter 2007; 23(10):231010.
10. Institute for Safe Medication Practices. New Fentanyl Warnings: More Needed to Protect Patients. Medication Safety Alert. Available at <http://www.ismp.org/newsletters/acutecare/articles/20050811.asp>. Accessed Nov 2010.
11. Institute for Safe Medication Practices. Ongoing, Preventable fatal Events with Fentanyl Transdermal Patches are Alarming! Medication Safety Alert. Available at <http://www.ismp.org/newsletters/acutecare/articles/20070628.asp>. Accessed Nov 2010.
12. U.S. Food and Drug Administration (FDA). MedWatch Safety Alerts for Human Medical Products. Information for Healthcare Professionals: Fentanyl Transdermal System (marketed as Duragesic and generics) (07/15/05). Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125844.htm>. Accessed Nov 2010.
13. Health Canada. Med Effect. Duragesic Safety Information. Available at <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164429.pdf>.
14. e-CPS. BuTrans Monograph. <https://www.e-therapeutics.ca/cps.showMonograph.action?simpleMonographId=m702035>. Accessed Nov 2010.
15. Regier, L. RxFiles Q&A summary: buprenorphine transdermal patch. Saskatoon SK: Saskatoon Health Region; 2010 Sept. Available from www.rxfiles.ca. Accessed Dec 2010.
16. Argoff C. Optimal Pain Management in Older Patients. Medscape Neurology & Neurosurgery. Posted Oct 19, 2010. Available at <http://www.medscape.com/viewarticle/730074>. Accessed Dec 2010.