Opioids for Chronic Non-Cancer Pain (CNCP) Management in the Elderly [1,2,3]

Introduction

- There are several reasons why treating CNCP in the elderly is particularly difficult:
  - Clinical direction is lacking for the appropriate use of opioids in the elderly for CNCP.
  - Age related changes such as ↓ renal function, ↑ in body fat (which may affect how long a lipid-soluble substance stays in the body), and ↓ albumin levels may lead to higher or prolonged drug levels and more adverse events (AE).
- Note: the term "elderly" may be better thought of in terms of physiologic age (extent of age related morbidity), not just chronologic age.
- Opioids are an option for CNCP when other alternatives are ineffective, contraindicated or not tolerated.
- Don't forget about the importance of non-drug interventions to relieve pain/suffering and improve function where possible. {e.g. for osteoarthritis (OA): exercise, physical therapy & weight loss; also address any psycho-social issues e.g. mood, relationship, spiritual}

What are the risks or potential problems when using opioids in the elderly?

- CNS effects: related to recent dosage change, total dose and concomitant drugs with similar adverse effects.
  - Over-sedation, cognitive dysfunction (morphine: may impair for up to 7 days after dose increase[4])
- GI effects: increased risk of constipation and bowel obstruction in population where this is already common.
- Fall & Fracture: rates increased; recent observational cohort trial indicated there was significant rates of composite fracture for opioids versus NSAIDs (HR 4.47 95%CI 3.12 to 6.41); fall rate was also elevated (HR 1.64 95% CI 1.09 to 2.47). {Mortality and CV events also increased (HR mortality: 1.87 95% CI 1.39 to 2.53; HR CV risk: 1.77 95% 1.39-2.24.) but due to nature of the observational trial, uncertainty if this is a true causation or due to confounding. See Solomon Trial Summary [5]}
- Polypharmacy results in both pharmacodynamic and pharmacokinetic drug interactions (DIs).
- Elderly opioid users may unwittingly become targets for those involved in opioid abuse, diversion and trafficking.

What precautions should be taken for a more cautious opioid initiation in the elderly?

- Start with low doses: e.g. no more than **50% of the suggested initial dose** for adults. Consider longer dosing intervals.[3]
  - morphine po: 2.5-5mg q6h, q8h or q12h (in elderly) [vs 5-10mg q4h prn (adult)]
  - hydromorphone po: 0.5-1mg q6h, q8h or q12h (in elderly) [vs 1-2mg po q4h (adult)]
- Use slow titration to find optimal dose; time interval between dose increases should be longer.
- More frequent monitoring; consider a **3 day tolerance check** i.e contact patient within 3 days of starting/changing dose to assess.[3]
- **Reassess benzodiazepines** & other CNS sedatives. If possible taper[6] &/or discontinue (to ↓ risk of falls & cognitive impairment)[3,7].
- **Be proactive in preventing constipation.** {e.g. hydration, dietary fiber (not a fiber laxative), laxative (senna, PEG, lactulose, bisacodyl)}

What are some pros and cons to various analgesics in the elderly?

	Drug Elderly dose considerations	Pro	Con
Analgesic [8]	**Acetaminophen** ⇨ max 4g/day; consider limiting to ≤ 3.25g/day ⇨ monophasic (4-6hr) & bi-phasic (6-8hr) formulations	♦ If effective, relatively safe unless patient has hepatic dysfunction ♦ less GI (ulcer) and less renal toxicity than NSAIDS	♦less effective than NSAIDS for OA pain (not function) **but** less GI AEs (e.g. ulcer)[9] ♦caution with max dose & long-term use; risk of liver toxicity (e.g. with prolonged use, high doses, alcohol overuse)
NSAIDs [8] ⇨if ↑↑ GI risk, +/- PPI or misoprostol	**Naproxen** 220OTC; 250-375mg BID	♦ May have less CV AEs; low cost	♦ ?DI with ASA
	Ibuprofen 400-600mg TID	♦ Low cost	♦ DI with ASA; stroke concern? meta?
	Celecoxib 100-200mg daily	♦ Possibly less GI ulcer/bleed	♦ Higher cost
Opioid [10] ⇨lower risk of end-organ damage such as GI, renal or hepatic toxicity ⇨Consider opioid rotation if AEs; use ~ 50% of equivalent dose to account for incomplete cross tolerance	**Codeine** +/- acetamin-ophen	♦There is debate on codeine's role in elderly. Evidence lacking; AEs common. ♦Be alert for potential overuse of acetaminophen in combination products. ♦Tramadol: effect for pain is small to moderate; effect on function is small. While it avoids some of the potential GI & renal issues with NSAIDs, and has a limited opioid effect relative to strong opioids, it causes more somnolence & CNS AEs than both placebo &/or NSAIDs. DIs: quite a few. Somewhat high cost. Useful for some, but also some disadvantages.	♦ +++ constipation ♦ Requires conversion to morphine; may not be as effective in certain patients 2D6
	Tramadol +/- acetamin-ophen		♦ Max dose 300mg/day for age >75yrs ♦ DIs: serotonergic drugs e.g. SSRIs; possible serotonin syndrome; seizures; CYP-2D6
	Buprenorphine patch[11]	♦ Weak/partial opioid	♦ Skin irritation
	Morphine	♦ Strong opioid; reasonable if tolerated.	♦ Avoid in renal failure as may result in accumulation of toxic metabolite (M6G)
	Hydromorphone **Oxycodone** +/- acetaminophen in combo products	♦ Strong opioids: hydromorphone, oxycodone: ? less problems with constipation & sedation?	♦ Hydromorphone 0.5-1mg q8-12h sometimes adequate for some
	Fentanyl patch (usually q72hr application, then remove; drug absorbed into skin reservoir, then into circulation)	♦ Strong opioid. Less constipation than oxycodone (oxycodone SR pts >65yrs are 7.33 x more likely to have constipation than fentanyl pts)[12]	♦ High potency; not for opioid naïve; high overdose risk; limited titration ability ♦ DIs: CYP-3A4 ♦heat ↑ effect & risk

AE=adverse effect CNS=central nervous system CV=cardiovascular CYP=cytochrome p450 enzyme interactions DI=drug interactions fx=function GI=gastrointestinal OA=osteoarthritis PEG=polyethylene glycol PPI=proton pump inhibitor pt=patients

Opioid Agonists: Considerations in the Elderly in CNCP

Weak or Partial Opioids	Initial / Low Dose	Comments
Codeine +/- acetaminophen	15-30mg po q4-6h (dose limiting ceiling effect at >60mg/dose)	◆ requires conversion to morphine via CYP-2D6; less effective in patients with reduced metabolism due to genetic factors or if on 2D6 inhibitors*.[26] ◆ codeine alone is a weak analgesic with very limited effectiveness.[15] Combination with **acetaminophen** increases analgesic efficacy; however limit acetaminophen to ≤4g/day (ideally ≤3.2g/day) to reduce hepatic risk[2]. The caffeine content of some products may be problematic (stimulation, diuresis). ◆ adverse effects (e.g. constipation) may be more common than other opioids
Codeine CR	50mg po q12h (may consider low doses of strong opioids if >200mg/day)	
Tramadol +/- acetaminophen	37.5mg po q6h (max 8 tablets/day)	◆ metabolized by CYP-2D6; less effective in patients with reduced metabolism due to genetic factors or if on 2D6 inhibitors* ◆ weak opioid, but effect also from ↑ in serotonin and norepinephrine; high cost ◆ caution with other serotonergic drugs & drugs that ↓ seizure threshold ◆ CNS SE: somnolence; suggested max dose 300mg/day for age >75yrs
Tramadol CR (given q24h)	100-150mg po daily	
Buprenorphine patch[27]	5mcg/hr q7days (max 20mcg/hr)	◆ partial opioid agonist; metabolized by CYP-3A4**. ◆ skin irritation common ◆ long & delayed action; allow ≥3 days for steady state levels and effect ◆ hepatic metabolism; not affected by decline in renal function; high cost ◆ ↓ abuse potential & ↓ withdrawal than fentanyl; may initiate in opioid naïve
Strong Opioids	**Initial / Low Dose**	**Comments**
Morphine IR	2.5-5mg po q4-6-8h	◆ morphine syrup useful for initiating & titrating lowest dosages in elderly ◆ in renal dysfunction: use reduced dose, or if severe impairment, avoid use (metabolites M3G & M6G $_{active}$ may accumulate and cause toxicity)[20,21] ◆ various brand choices vary in dosage strengths available and cost[23,27] ◆ some CR capsule products (M-Eslon, Kadian) may be sprinkled onto food
Morphine CR (most given q12h, e.g. MS Contin, MOS-SR, M-Eslon) (Kadian given q24h)	10mg po q12h (this dose M-Eslon only) 15mg po q12h 10-20mg po q24h	
Hydromorphone IR	0.5-1mg po q4-6-8h	◆ a low dose of IR given q8-12h may often be adequate in the frail elderly ◆ may cause less constipation & sedation than morphine; more costly ◆ some CR capsule products (Hydromorph Contin) may be sprinkled onto food
Hydromorphone CR (Contin given q12h; Jurnista given q24h)	3mg po q12h 4mg po q24h	
Oxycodone +/- acetaminophen	2.5-5 mg po q4-6-8h (most tablets scored; allows for lower-dose or titration by ½ tab)	◆ metabolized by CYP-2D6; caution in renal or hepatic dysfunction as plasma concentrations may increase up to 50%. Also a kappa agonist. ◆ may cause less constipation & sedation than morphine; more costly ◆ CR formulation has a biphasic release (~38% initial & ~62% delayed release); inability to titrate the immediate release component separately may be problematic in some patients triggering subtle, early opioid withdrawal.
Oxycodone CR	5-10mg po q12h	
Fentanyl patch	12-25mcg/hr q72hr	◆ high potency; **not for opioid naïve** or those with poor response to codeine ◆ ↑overdose risk: heat ↑ absorption, effect & risk; CYP-3A4 inhibitors** ↑ risk ◆ onset delayed by 12-24hr. Allow ≥6 days prior to ↑ dose. Relatively high cost

IR=immediate release CR=controlled release, M3G=morphine-3-glucuronide M6G=morphine-6-glucuronide tab=tablet
CYP=Cytochrome P450 metabolic system [29]
*CYP-2D6 inhibitors include: amiodarone, bupropion, duloxetine, fluoxetine, paroxetine, ritonavir, ropinirole.
** CYP-3A4 inhibitors include: clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, verapamil
Additional information (including other formulations & new products) available from the RxFiles Opioid Comparison Chart online

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[3] Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain — Part B: Recommendations for Practice, Version 5.5 April 30, 2010. Accessed at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf. National opioid guideline website hosted at: http://nationalpaincentre.mcmaster.ca/opioid/ {Page 50-51 discuss some specific considerations for elderly patients.}
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