Opioids for chronic noncancer pain in the elderly
An osteoarthritis case

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Case description
Mrs Z.T. is a 74-year-old woman who comes to your office with increasing left knee pain. Prior investigations have confirmed she has osteoarthritis (OA). She follows her physiotherapist's exercise advice, and she takes 650 mg of acetaminophen 4 times a day. Two months ago Mrs Z.T. added 400 mg of ibuprofen 3 times a day, as she was unable to do her laundry, houseclean, or shop for groceries owing to the worsening pain. Mrs Z.T. has stopped doing aquatic exercise and notes she is not sleeping as well as usual. She uses a menthol topical rub at bedtime and has tried using a cold pack, with limited benefit. She is worried about taking ibuprofen owing to a history of stomach problems, for which she takes 20 mg of omeprazole daily. Previous 3-month trials of both topical nonsteroidal anti-inflammatory drugs (NSAIDs) and glucosamine were ineffective. She volunteers that she is ready to see the surgeon, which she was reluctant to consider in the past. Her medical history includes hypertension, which is treated with 12.5 mg of hydrochlorothiazide daily, and a gastric ulcer she had 10 years ago. She has no known allergies but has previously experienced nausea and constipation with Tylenol No. 3. Each morning she takes a multivitamin, 1000 IU of vitamin D, and 500 mg of elemental calcium. She is a nonsmoker and has an occasional glass of wine. There is no history of personal or family misuse of alcohol or other drugs as assessed and documented with the opioid risk tool.1,2

On examination, her blood pressure is 140/92 mm Hg (higher than her past few readings) and her pulse is 80 beats per minute. She is 162 cm tall and weighs 80 kg (body mass index of 30.5 kg/m²). She rates her pain as 8 of 10 when active, and 5 of 10 at rest. She walks using a cane; a limp is present. Her left knee examination results are unchanged. Previous x-ray scans showed severe degenerative changes. Laboratory investigation results are essentially normal, with a serum creatinine (SCR) level of 90 μmol/L (normal 45 to 110 μmol/L). Her estimated creatinine clearance (CrCl) rate is between 40 and 60 mL/min. While waiting for the results of her orthopedic assessment, Mrs Z.T. thinks she cannot manage with her present pain level and wants to try stronger medication.

Bringing evidence to practice
• Persistent pain and its inadequate treatment is associated with a number of adverse outcomes in older people, including functional impairment, falls, slow rehabilitation, muscle deconditioning, mood changes, decreased socialization, sleep and appetite disturbance, and greater health care use and costs.1 The drug treatment of pain has its own array of potential benefits and harms and must be individualized for optimal patient care. It is important to help the patient set realistic expectations and goals for improvement of both pain and function.2
• Non-drug therapies (eg, exercise, weight loss, cold pack treatments), acetaminophen, and NSAIDs are all effective options in managing the pain of OA. Nonsteroidal anti-inflammatory drugs are slightly more effective than acetaminophen; however, they are often considered second-line treatment owing to a higher risk of adverse gastrointestinal, renal, and cardiovascular events.1,3,4
• Local injection of either steroid or viscosupplementation might be an option for some, especially if the pain is in a single joint. A multimodal approach that includes a combination of drug and nondrug interventions is often most beneficial.
• Opioids might be suitable for OA when other therapies are inadequate, contraindicated, or not tolerated. (Tables 1,2,5-13 and 2,5,7,10,13-16 provide an overview of opioids.*) Evidence from randomized controlled trials suggests opioids have a small to moderate effect on pain and function in OA when compared with placebo.17,18 This benefit must be weighed against the potential harms associated with opioids.
• A recent observational trial of healthy older adults with arthritis found that, compared with NSAIDs, opioids were associated with a much higher risk of composite fracture (eg, hip, humerus, pelvis, wrist; hazard ratio [HR] = 4.47; 95% confidence interval 3.12 to 6.41) and bowel obstruction (HR = 4.87; 95% confidence interval 1.40 to 17.02).19,20 Cardiovascular events and all-cause mortality were also slightly elevated in the opioid group; however, given the limitations of the study and the modest HRs (eg, less than 2), these findings might be the result of confounding and not represent true causality.

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*The full version of the RxFiles Opioid Comparison chart is available at www.cfp.ca. Go to the full text of the article online, then click on CFPplus in the menu at the top right-hand side of the page.
When prescribing opioids to elderly patients, consider

- Review the patient’s medication history. This is very useful in assessing concurrent or undisclosed use of medications, such as over-the-counter NSAIDs, other opioids, and benzodiazepines or other sedatives, that place patients at higher risk for morbidity or mortality. Checking the provincial electronic prescription records, if available, is particularly useful. Assessment of the patient’s ability to reliably self-administer should also be considered, especially if signs of cognitive impairment are apparent and he or she is still living independently. Adherence aids (eg, bubble packs, reminders, dosettes), home care, or supervised medication administration might be beneficial.

- Use tools to assess risk. The opioid risk assessment needs to consider that elderly patients living in high-risk environments might become targets for opioid misuse or diversion. Additional prescribing information and tools will be useful in addressing any patient or physician concerns about opioid risks, about what to expect from therapy, and about managing any adverse effects. Consider use of a treatment agreement and informed consent before or during initiation of an opioid trial. Particular issues that are important for elderly patients or their caregivers include issues such as secure storage and safe medication management. “Universal precautions” for opioid pain management (discussed in detail elsewhere) are useful in assessing and managing risk and improving patient care. The opioid risk tool is one validated option recommended for assessing opioid risk based on 5 general risk factors for future aberrant opioid-related behaviour.

- Consider weak opioids, such as codeine or tramadol, as the first opioid step in the treatment of mild to moderate OA pain. Both are available alone or in combination with acetaminophen and are comparable to NSAIDs for analgesic efficacy. Other factors that might affect the choice of medication include side effects (such as constipation with codeine), higher costs, lack of drug plan coverage, and increased risk of drug interactions with tramadol. Using low doses

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Table 1. Weak or partial opioid agonists: Considerations in the elderly with chronic noncancer pain.

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<tr>
<th>DRUG</th>
<th>INITIAL LOW DOSE</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td>Codeine, with or without</td>
<td>15-30 mg orally</td>
<td>• Requires conversion to morphine via CYP 2D6; less effective in patients</td>
</tr>
</tbody>
</table>
| acetaminophen              | every 4-6 h (dose-| with reduced metabolism owing to genetic factors or if using 2D6 inhibitors*
|                           | limiting ceiling | • Codeine alone is a weak analgesic with very limited effectiveness
|                           | effect at >60 mg | • Combination with acetaminophen increases analgesic efficacy; however, limit
|                           | per dose)        | acetaminophen to ≤ 4 g/d (ideally ≤ 3.2 g/d) to reduce hepatic risk
| Codeine CR                 | 50 mg orally     | • Caffeine content of some products might be problematic (stimulation,     |
|                           | every 12 h       | diuresis)                                                                |
|                           | (consider low doses | • Adverse effects (eg, constipation) might be more common than with other  |
|                           | of stronger opioid if ≥ 200 mg/d) | opioids                                                                  |
| Tramadol, with or without  | 37.5 mg orally   | • Metabolized by CYP 2D6 to active metabolite; less effective in patients   |
| acetaminophen              | every 6 h (maximum | with reduced metabolism owing to genetic factors or if using 2D6 inhibitors* |
|                           | 8 tablets daily) | • Weak opioid but also some effect from an increase in serotonin and      |
| Tramadol CR (given every 24 | 100-150 mg/d orally | norepinephrine                                                           |
| h)                        |                  | • High cost                                                               |
|                           |                  | • Caution with other serotoninergic drugs and drugs that decrease seizure  |
|                           |                  | threshold                                                                |
|                           |                  | • Central nervous system side effects including somnolence               |
|                           |                  | • Suggested maximum dose of 300 mg/d for those older than 75 y            |
| Buprenorphine patch       | 5 µg/h every 7 d | • Partial opioid agonist; metabolized by CYP 3A4,† as skin irritation is common |
|                           | (maximum 20 µg/h) | • Long and delayed action available; allow ≥ 3 d for steady state levels   |
|                           |                  | and effect                                                                |
|                           |                  | • Hepatic metabolism; not affected by decline in renal function           |
|                           |                  | • High cost                                                                |
|                           |                  | • Decreased abuse potential and decreased withdrawal than with fentanyl; may |
|                           |                  |   be initiated in opioid-naïve patients                                    |

CR—controlled release, CYP—cytochrome P450, IR—immediate release, M3G—morphine-3-glucuronide, M6G—morphine-6-glucuronide.

*Cytochrome P450 2D6 inhibitors include amiodarone, bupropion, duloxetine, fluoxetine, paroxetine, ritonavir, and ropinirole.
†Cytochrome P450 3A4 inhibitors include clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, and verapamil.
Data from National Opioid Use Guidelines Group; Stone and Regier; The Oxford League Table of Analgesic Efficacy; Department of Veterans Affairs and Department of Defense; Smith, Regier; Michael G. DeGroote National Pain Centre, MacDonald and Macleod, Regier, Flockhart.
of stronger opioids might be considered, especially if weak opioids are ineffective, drugs are not tolerated, or if pain is considered severe. While there is an increased risk of adverse events, these are usually reversible with discontinuation and should not preclude a trial. 28

-Start with a lower opioid dose (approximately 50% of a usual initial adult dose) and titrate more slowly than for a younger adult. A 3-day tolerance check is recommended after initiation or dose increase to assess for excess sedation and efficacy. 2 This can be done by way of a telephone call, and it allows the physician, pharmacist, or nurse to check for toleration, especially noting any excess sedation or confusion.

-Incorporate an appropriate bowel regimen, as this is essential in preventing constipation. Laxatives will usually be necessary. Polyethylene glycol and lactulose have more evidence for efficacy; however, other choices such as senna or bisacodyl might be considered on the basis of an individual patient’s symptoms, toleration, and preferences. 29 Docusate sodium is generally ineffective. 29,30

### Case description: part 2

A 2.5-mg dose of morphine liquid orally every 6 hours was initiated, with gradual dose titration, for Mrs Z.T.’s pain. After 10 weeks, she achieved a dose of 7.5 mg every 6 hours. Mrs Z.T. was then switched to 15 mg of long-acting morphine every 12 hours. Her pain scores decreased to 3 of 10, and she appeared to tolerate the opioid well. The ibuprofen was stopped, but 650 mg of acetaminophen was occasionally useful. A 15-mL dose of lactulose orally twice daily, in addition to 2 senna tablets by mouth daily as needed, was effective for preventing constipation. Mrs Z.T. was also scheduled for surgery.

### Nine months later

Today Mrs Z.T.’s daughter brings her to your office

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**Table 2. Strong opioid agonists: Considerations in the elderly in chronic noncancer pain.**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INITIAL LOW DOSE</th>
<th>COMMENTS</th>
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<tbody>
<tr>
<td>Morphine IR</td>
<td>2.5-5 mg orally every 4-8 h</td>
<td>- Morphine syrup useful for initiating and titrating lowest doses in the elderly&lt;br&gt;- In renal dysfunction, use reduced dose or avoid use if impairment is severe (active metabolites M3G and M6G can accumulate and cause toxicity) 8-14,15&lt;br&gt;- Brand choices vary in available dosage strengths and in cost 9,16</td>
</tr>
<tr>
<td>Morphine CR</td>
<td>10 mg orally every 12 h (this dose is for M-Eslon only)&lt;br&gt;15 mg orally every 12 h&lt;br&gt;10-20 mg orally every 24 h</td>
<td>- A low dose of IR given every 8-12 h might often be adequate in the frail elderly&lt;br&gt;- Might cause less constipation and sedation than morphine&lt;br&gt;- More costly&lt;br&gt;- Some CR capsule products (M-Eslon, Kadian) can be sprinkled onto food</td>
</tr>
</tbody>
</table>
| Hydromorphone IR | 0.5-1mg orally every 4-8 h | - Metabolized by CYP 2D6*; use with caution in renal or hepatic dysfunction, as plasma concentrations might increase up to 50%
- Also a k agonist<br>- Might cause less constipation and sedation than morphine<br>- More costly<br>- CR formulation has a biphasic release (approximately 38% initial release, and approximately 62% delayed release); inability to titrate the IR component separately might be problematic in some patients, triggering subtle, early opioid withdrawal |
| Hydromorphone CR | 3 mg orally every 12 h<br>4 mg orally every 24 h | - A low dose of IR given every 8-12 h might often be adequate in the frail elderly<br>- Might cause less constipation and sedation than morphine<br>- More costly<br>- Some CR capsule products (Hydromorph Contin) can be sprinkled onto food |
| Oxycodone, with or without acetaminophen | 2.5-5 mg orally every 4-8 h (most tablets scored; allows for lower dose or titration by half tablets) | - High potency; not for opioid-naïve patients or those with poor response to codeine<br>- Overdose risk: heat absorption, effect, and risk; CYP 3A4 inhibitors’ risk<br>- Onset delayed by 12-24 h<br>- Allow ≥ 6 d before increasing dose<br>- Relatively high cost |
| Oxycodone CR | 5-10 mg orally every 12 h | - Also a k agonist<br>- Might cause less constipation and sedation than morphine<br>- More costly |
| Fentanyl patch | 12-25 µg/h every 72 h | - High potency; not for opioid-naïve patients or those with poor response to codeine<br>- Overdose risk: heat absorption, effect, and risk; CYP 3A4 inhibitors’ risk<br>- Onset delayed by 12-24 h<br>- Allow ≥ 6 d before increasing dose<br>- Relatively high cost |

CR—controlled release, CYP—cytochrome P450, IR—immediate release, M3G—morphine-3-glucuronide, M6G—morphine-6-glucuronide.
*Cytochrome P450 2D6 inhibitors include amiodarone, bupropion, duloxetine, fluoxetine, paroxetine, ritonavir, and ropinirole.
†Cytochrome P450 3A4 inhibitors include clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, and verapamil.
Data from Stone and Regier; 7 Department of Veterans Affairs and Department of Defense; 8 Smith; 9 Regier; 10 Michael G. DeGroote National Pain Centre, 13 Flockhart, 14 RPHWorld.com, 15 Peterson et al, 16 Regier and Jensen. 16
concerned that during the past few days her mother has become drowsy and confused. Last week, Mrs Z.T. had 2 days of vomiting, diarrhea, and fever, which resolved after a return to her usual diet. Mrs Z.T. denies other complaints, and says that most of the time her knee pain is 3 or 4 of 10. She is aware she is in an office but is unable to tell you the date or season. And she does not recognize your clinic nurse whom she has known for years. The remainder of the examination is unremarkable. Investigations including chest x-ray scan, electrocardiogram, urinalysis, thyroid-stimulating hormone levels, and complete blood count and electrolyte measurements reveal normal results. Her serum urea and SCr levels are 10.4 mmol/L and 135 µmol/L, respectively. Her estimated CrCl rate is between 28 and 40 mL/min.

**Bringing evidence to practice**

- Risk of delirium from opioids, especially with opioids predominantly renally excreted, increases as CrCl rates worsen. This can happen with acute causes of reduced renal function (eg, dehydration or drug interactions such as with NSAIDs and angiotensin-converting enzyme inhibitors). Other causes of delirium, such as patients taking their medications incorrectly, should also be explored.
- Remember that renal function in the elderly is often lower than expected based on the SCr levels alone. Thus, it is essential to estimate the CrCl rate or estimated glomerular filtration rate using one of the available calculators. Whether to use actual body weight, ideal body weight, or something in between is controversial; however, ideal body weight is usually recommended and provides a more conservative estimate.
- Adverse effects from morphine are thought to relate to the morphine-6-glucuronide and morphine-3-glucuronide metabolites, which might accumulate in renal dysfunction. There is little evidence for a specific degree of renal impairment at which morphine should be avoided; however, one source suggests a CrCl rate less than 30 mL/min. At low doses, many elderly patients will tolerate morphine. If adverse effects do occur, they might resolve with a switch to hydromorphone, oxycodone, or fentanyl.
- To switch opioids, calculate an equivalent dose and then reduce by 25% to 50% to account for the incomplete cross-tolerance often seen upon switching. Regardless of the dose chosen, remember to reassess early (within 3 days) and adjust dose as necessary. Note that patients taking codeine or tramadol with little or no pain relief should be considered opioid naïve when switching. Both medications require metabolic conversion to their active metabolite for their full effect, and some people have reduced metabolism owing to genetics or other drugs.
- The role of supplemental short-acting opioids in “as needed for breakthrough pain” situations or pain exacerbations in chronic noncancer pain is controversial. Routine use in chronic noncancer pain is often discouraged to minimize adverse effects and psychological dependence. When warranted, as-needed dosing for incidental pain should be used sparingly. It will often be useful to assist during the titration phase or when switching opioids. Frequent pain exacerbation at the end of the dosing interval might require a change in the dose or frequency of administration of the regularly scheduled regimen. When supplemental dosing is used, giving 10% to 15% of the total daily opioid dose every 4 hours as needed is a commonly accepted approach.

**Case description: part 3**

Mrs Z.T.’s renal function might recover following the acute gastrointestinal illness, but to prevent further episodes, the opioid is switched to 1 mg of immediate-release hydromorphone every 8 hours, with 0.5 mg every 4 hours as needed for breakthrough pain. This dose is effective and well tolerated overall, with
only 1 breakthrough dose required on days when she does housecleaning activities. Conversion to a long-acting product was discussed, but Mrs Z.T. believes she is functioning well. Cognitive function is improved. Mrs Z.T. awaits surgery. Special consideration will be needed to manage “acute on chronic pain” at the time of pain followed by an opioid taper and discontinuation.

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