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/m^2). 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]
- Nondrug 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 **CFPlus** in the menu at the top right-hand side of the page.

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

DRUG	INITIAL LOW DOSE	COMMENTS
Codeine, with or without acetaminophen Codeine CR	15-30 mg orally every 4-6 h (dose-limiting ceiling effect at >60 mg per dose) 50 mg orally every 12 h (consider low doses of stronger opioid if >200 mg/d)	• Requires conversion to morphine via CYP 2D6; less effective in patients with reduced metabolism owing to genetic factors or if using 2D6 inhibitors*[8,11] • Codeine alone is a weak analgesic with very limited effectiveness[6] • Combination with acetaminophen increases analgesic efficacy; however, limit acetaminophen to ≤4 g/d (ideally ≤3.2 g/d) to reduce hepatic risk[2] • Caffeine content of some products might be problematic (stimulation, diuresis) • Adverse effects (eg, constipation) might be more common than with other opioids
Tramadol, with or without acetaminophen Tramadol CR (given every 24 h)	37.5 mg orally every 6 h (maximum 8 tablets daily) 100-150 mg/d orally	• Metabolized by CYP 2D6 to active metabolite; less effective in patients with reduced metabolism owing to genetic factors or if using 2D6 inhibitors* • Weak opioid but also some effect from an increase in serotonin and norepinephrine • High cost • Caution with other serotonergic 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[12]	5 µg/h every 7 d (maximum 20 µg/h)	• Partial opioid agonist; metabolized by CYP 3A4,† as skin irritation is common • 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,[2] Stone and Regier,[5] *The Oxford League Table of Analgesic Efficacy*,[6] Department of Veterans Affairs and Department of Defense,[7] Smith,[8] Regier,[9] Michael G. DeGroote National Pain Centre,[10] MacDonald and MacLeod,[11] Regier,[12] Flockhart.[13]

- When prescribing opioids to elderly patients, consider the following.
  -Consider the treatment as a trial.[2,21] Taking the time to document a patient's current and desired goals for pain and function will be useful in evaluating whether the opioid is effective (eg, definite benefits and reasonable tolerability).
  -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.[2,22] 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.[5] 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[23,24] and informed consent[25] before or during initiation of an opioid trial.[2] 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.[26,27] 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.[1,2]
  -Consider weak opioids, such as codeine or tramadol, as the first opioid step in the treatment of mild to moderate OA pain.[2] Both are available alone or in combination with acetaminophen and are comparable to NSAIDs for analgesic efficacy.[6] 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

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

DRUG	INITIAL LOW DOSE	COMMENTS
Morphine IR Morphine CR (most given every 12 h, eg, MS Contin, MOS SR, M-Eslon; Kadian given every 24 h)	2.5-5 mg orally every 4-8 h 10 mg orally every 12 h (this dose is for M-Eslon only) 15 mg orally every 12 h 10-20 mg orally every 24 h	• Morphine syrup useful for initiating and titrating lowest doses in the elderly • 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] • Brand choices vary in available dosage strengths and in cost[9,16] • Some CR capsule products (M-Eslon, Kadian) can be sprinkled onto food
Hydromorphone IR Hydromorphone CR (Contin given every 12 h; Jurnista given every 24 h)	0.5-1mg orally every 4-8 h 3 mg orally every 12 h 4 mg orally every 24 h	• A low dose of IR given every 8-12 h might often be adequate in the frail elderly • Might cause less constipation and sedation than morphine • More costly • Some CR capsule products (Hydromorph Contin) can be sprinkled onto food
Oxycodone, with or without acetaminophen Oxycodone CR	2.5-5 mg orally every 4-8 h (most tablets scored; allows for lower dose or titration by half tablets) 5-10 mg orally every 12 h	• Metabolized by CYP 2D6*; use with caution in renal or hepatic dysfunction, as plasma concentrations might increase up to 50% • Also a κ agonist • Might cause less constipation and sedation than morphine • More costly • 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
Fentanyl patch	12-25 μg/h every 72 h	• High potency; not for opioid-naïve patients or those with poor response to codeine • Overdose risk: heat absorption, effect, and risk; CYP 3A4 inhibitors† risk • Onset delayed by 12-24 h • Allow ≥ 6 d before increasing dose • 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,[5] Department of Veterans Affairs and Department of Defense,[7] Smith,[8] Regier,[9] Michael G. DeGroote National Pain Centre,[10] Flockhart,[13] RPHWorld.com,[14] Peterson et al,[15] Regier and Jensen.[16]

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

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.[14,31] 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 (**Table 2**).[5,7-10,13-16] 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.[32] 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.[2] Regardless of the dose chosen, remember to reassess early (within 3 days) and adjust dose as necessary.[2] 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 (**Table 1**).[2,5-13]
- The role of supplemental short-acting opioids in "as needed for breakthrough pain" situations or pain exacerbations in chronic noncancer pain is controversial.[7] 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 surgery followed by an opioid taper and discontinuation.

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References

1. American Geriatrics Society (AGS) Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009;57(8):1331-46. Epub 2009 Jul 2. Available from: **www.americangeriatrics.org/files/documents/2009_Guideline.pdf**. Accessed 2011 Apr 13.
2. National Opioid Use Guidelines Group. *Canadian guideline for safe and effective use of opioids for chronic non-cancer pain—part B: recommendations for practice.* Version 5.5. Hamilton, ON: National Opioid Use Guidelines Group; 2010. Available from: **http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf**. Accessed 2011 Jun 6.
3. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2007;66(4):433-9. Epub 2007 Jan 4.
4. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2003;(2):CD004257.
5. Stone S, Regier L. *RxFiles Q&A summary: opioids for chronic non-cancer pain (CNCP) management in the elderly*. Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/Opioids-Pain-ELDERLY-QandA.pdf**. Accessed 2011 Apr 13.
6. *The Oxford League table of analgesic efficacy*. Oxford, UK: Bandolier; 2007. Available from: **www.medicine.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/lftab.html**. Accessed 2011 Apr 13.
7. Department of Veterans Affairs, Department of Defense. *Clinical practice guideline for management of opioid therapy for chronic pain.* Washington, DC: US Department of Veterans Affairs; 2011. Available from: **www.healthquality.va.gov/COT_312_Full-er.pdf**. Accessed 2011 Apr 13.
8. Smith HS. Opioid metabolism. *Mayo Clin Proc* 2009;84(7):613-24.
9. Regier L. Opioid analgesic comparison chart. In: *RxFiles drug comparison charts.* 8th ed. Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Opioid.pdf**. Accessed 2011 Apr 13.
10. Michael G. DeGroote National Pain Centre. *Opioid manager tool.* Hamilton, ON: Michael G. DeGroote National Pain Centre; 2011. Available from: **http://nationalpaincentre.mcmaster.ca/opioidmanager/**. Accessed 2011 Apr 13.
11. MacDonald N, MacLeod SM. Has the time come to phase out codeine? *CMAJ* 2010;182(17):1825.
12. Regier L. *RxFiles Q&A: BuTrans patch—buprenorphine transdermal system (BTDS) for weekly application*. Saskatoon, SK: RxFiles; 2010. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/BuTrans-QandA.pdf**. Accessed 2011 Apr 13.
13. Flockhart DA. *Drug interactions: cytochrome P450 drug interaction table.* Indianapolis, IN: Indiana University School of Medicine; 2007. Available from: **http://medicine.iupui.edu/clinpharm/ddis/table.asp**. Accessed 2011 Mar 29.
14. RPHWorld.com [website]. *Creatinine clearance calculator.* RPHWorld.com; 2011. Available from: **www.rphworld.com/pharmacist/viewlink-25224.html**. Accessed 2011 Apr 13.
15. Peterson GM, Randall CT, Paterson J. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur J Clin Pharmacol* 1990;38(2):121-4.
16. Regier L, Jensen B. Opioids in chronic non-cancer pain (CNCP). *RxFiles Newsletter* 2011 Mar. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/Opioid-2011-Newsletter.pdf**. Accessed 2011 Apr 13.
17. Nüesch E, Rutjes AW, Husni E, Welch V, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database Syst Rev* 2009;(4):CD003115.
18. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database Syst Rev* 2006;(3):CD005522.
19. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med* 2010;170(22):1968-76.
20. Regier L. *RxFiles trial summary: the comparative safety of analgesics in older adults with arthritis.* Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/Pain-Trial-Summary-Solomon-Elderly-Arthritis.pdf**. Accessed 2011 Apr 12.
21. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009;10(2):113-30.
22. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing* 2011;40(1):23-9. Epub 2010 Nov 9.
23. McMaster University [website]. *Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Appendix B-5: sample opioid medication treatment.* Hamilton, ON: McMaster University; 2011. Available from: **http://nationalpaincentre.mcmaster.ca/opioid.** Accessed 2011 June 15**.**
24. RxFiles [website]. *Sample patient agreement for long-term opioid therapy*. Saskatoon, SK: RxFiles; 2008. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.pdf**. Accessed 2011 Apr 13.
25. RxFiles [website]. *Informed consent for the use of opioid medication*. Saskatoon, SK: RxFiles; 2008. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.docx**. Accessed 2011 Apr 13.
26. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med* 2005;6(2):107-12.
27. Regier L. Substance abuse/addiction: overview and treatment considerations. In: *RxFiles drug comparison charts.* 8th ed. Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/CHT-Substance-Abuse.pdf**. Accessed 2011 Apr 13.
28. Dalhousie Academic Detailing Service. *Opioids in chronic non-cancer pain—workbook.* Halifax, NS: Dalhousie University; 2010. Available from: **http://cme.medicine.dal.ca/files/ADS_opioids.pdf**. Accessed 2011 Apr 13.
29. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol* 2005;100(4):936-71.
30. Hurdon V, Viola R, Schroder C. How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill. *J Pain Symptom Manage* 2000;19(2):130-6.
31. National Kidney Foundation. *GFR calculator.* New York, NY: National Kidney Foundation; 2000. Available from: **www.kidney.org/professionals/KLS/gfr_calculator.cfm**. Accessed 2011 Apr 13.
32. York Teaching Hospital [website]. *Palliative care analgesic dose conversion chart.* York, UK: York Teaching Hospital; 2011. Available from: **www.yacpalliativecare.com/documents/download71.pdf**. Accessed 2011 Apr 13.