Multiple opioids in pain management

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Karl, an 84-year-old man, has chronic pain from osteoarthritis of both hips. He also has type 2 diabetes mellitus, coronary artery disease, class III congestive heart failure (using the New York Heart Association classification system), and mild renal failure with an estimated glomerular filtration rate of 45 mL/min per 1.73 m². He is a high-risk candidate for bilateral arthroplasty and has decided against surgery if the pain can be controlled enough to allow him mobility around his house. He has marked fatigue from his heart failure and hasn’t been independently walking outside his home for several years.

He and his wife live together in a small house. Karl held various jobs throughout his life, including in mining and logging. He smoked 1 pack per day for 30 years before quitting 15 years ago. He does not drink alcohol.

Karl’s pain management has been a challenge. He needed more than 8 Tylenol No. 3 tablets daily, so he was prescribed sustained-release codeine. Despite a dose of 200 mg every 8 hours with breakthrough doses of Tylenol No. 4 twice daily, his pain was not controlled. Gabapentin was added as an adjuvant pain medication, and Karl was able to tolerate a 300-mg dose 3 times daily.

One month later, his pain was still not adequately controlled, resulting in poor sleep and immobility. A 25-µg fentanyl transdermal patch every 72 hours was added to the sustained-release codeine. For breakthrough pain he was given 4 mg of hydromorphone to be used up to 4 times daily. Over the next month his use of the hydromorphone went up to almost 30 mg daily, so this was converted to sustained-release hydromorphone at 12 mg every 8 hours.

Over the past few weeks, Karl has increasingly complained of being confused and drowsy during the day and unable to sleep at night. He is experiencing muscle twitching all over. He is still complaining of pain in his hips and his back but there is no evidence of generalized pain, allodynia, or hyperalgesia.

Karl also uses the following medications: 750 mg of metformin twice daily, 81 mg of acetylsalicylic acid daily, 20 mg of ramipril daily, 40 mg of furosemide daily, and 50 mg of atenolol daily.

Karl’s symptoms are likely due to opioid-induced neurotoxicity. Opioid-induced neurotoxicity is a multifactorial syndrome that causes a spectrum of symptoms from mild confusion or drowsiness to hallucinations, delirium, and seizures. It is extremely difficult to predict which opioid is responsible, as Karl is taking 3 different opioids. It also could be the interaction of his many other medications, relative dehydration due to his medications for heart failure, or some other cause of delirium.

Physicians prescribe multiple opioids for patients when trying to control complex pain and reach doses of opioids that are beyond their previous clinical experience. In Karl’s case, he had reached the maximum recommended dose of codeine and still had pain. Codeine has a maximum recommended dose of 600 mg daily, as it is dependent on the enzyme cytochrome P450 2D6 to metabolize it to norcodeine and to morphine, which is the actual analgesic. However, once the maximum recommended dose is reached, the drug should be changed to an opioid without a maximum dose rather than adding a second opioid.

Opioid titration

A cardinal rule of pain management is that opioids need to be titrated to achieve the best analgesia with the fewest side effects. Because all opioids, except for codeine, do not have a maximum dose, the right dose for each patient will be the balance between pain relief and side effects. The right dose is different for each individual, but in general, the younger the person the larger the dose. An option for Karl would have been to switch from codeine to another sustained-release opioid, such as hydromorphone, oxycodone, or fentanyl. With his mild renal failure, he is likely to get active metabolite accumulation when using higher doses of morphine, so it is best to use hydromorphone, oxycodone, or fentanyl.

Opioids need to be titrated up by percentages rather than fixed amounts. If pain is uncontrolled, the dose should be increased by about 25% of the total dose with each titration. For example, if Karl was switched to an equianalgesic amount of hydromorphone (600 mg of codeine/6 = 100 mg of morphine/5 = 20 mg hydromorphone daily) and despite increasing the dose to 36 mg daily he was still in pain, then his next dose would be 48 mg (36 x 0.25 = 9-mg increase, rounded to 48 mg for convenient dosing). If the dose is not adjusted upward in a percentage fashion, it could appear that the opioid...
is beginning to lose effectiveness at higher doses, causing the physician to consider adding another opioid.

Whenever the regular dose is increased, the breakthrough dose should also be increased. The breakthrough dose should be approximately 10% of the total daily dose given every 1 hour as needed.

Sustained-release opioids should give analgesia for 12 hours; if not, increase the dose rather than shorten the dosing interval. In most cases, shorten the dosing interval only if the patient experiences drowsiness for the first few hours of the 12-hour dose and yet has pain in the last few hours of the dose. Individuals younger than age 60 might also require a shorter dosing interval. Inappropriate shorter dosing intervals can lead to increased side effects.\(^3\)

**Continued pain**

Karl is taking 3 different opioids and his pain is still not controlled. There are several possible reasons for his continued pain:

- His pain might be severe enough that he requires a higher dose than all of the opioids are giving.
- His genetically determined liver enzymes might rapidly break down the opioids.
- He could have hyperalgesia, which is a rare side effect of large doses of opioids. If hyperalgesia was the cause, he would complain of his pain moving from his hips and back to all over his body, and he might also demonstrate allodynia (pain with non-painful stimuli).

Karl most likely has a genetic profile that is reducing the effectiveness of one or more of the opioids.\(^4\) Multiple alleles exist for all the opioid receptors as well as the metabolism enzymes and transport proteins. This will eventually explain what is seen clinically: the analgesia obtained and the side effects experienced with opioids have interindividual variation.

Karl used gabapentin as an adjuvant for his pain. Gabapentin is very effective for neuropathic pain, but it is not indicated as an adjuvant for all types of pain. Patients with neuropathic pain will report more hot, cold, or burning sensations, more surface pain with less dull and deep pain, and more distress with the pain, as compared with nonneuropathic pain.\(^5\)

**Management**

The best way to manage Karl’s pain is to switch from codeine to another sustained-release opioid and titrate to achieve the best analgesia with the fewest side effects. If Karl develops intolerable side effects or does not appear to get adequate relief with that opioid despite adequate titration, then he should be switched to another opioid, which should be titrated as tolerated.

Only with the transdermal fentanyl patch is there a need for a different opioid for the breakthrough medication. Otherwise, it is rare that people benefit from the use of 2 opioids simultaneously (an option that is best left to an experienced palliative care or pain physician). The only adjuvant that might benefit Karl would be acetaminophen. Nonsteroidal anti-inflammatory drugs are contraindicated with his cardiac and renal disease.

**Dr Gallagher** is a member of the Palliative Care Committee of the College of Family Physicians of Canada. She is Head of the Division of Residential Care and the Physician Program Director for Palliative Care at Providence Health Care and is a Clinical Professor in the Division of Palliative Care at the University of British Columbia in Vancouver.

**Competing interests**

Dr Gallagher accepts honoraria for education events sponsored by Purdue and has produced educational material for Bayer.

**References**


**BOTTOM LINE**

- There is no maximum dose for opioids except codeine.
- Titrate the dose to achieve the best analgesia with the fewest side effects. When titrating, increase the regular opioid dose by about 25%. Increase the breakthrough dose at the same time, using the guideline of 10% of the total daily dose given every 1 hour as needed.
- There is interindividual variation with the effects of opioids. Consider switching opioids if there is inadequate analgesia or intolerable side effects despite adequate titration.

**POINTS SAILLANTS**

- Il n’y a pas de doses maximales pour les opioïdes sauf pour la codeine.
- Dosez pour obtenir la meilleure analgésie avec le moins d’effets secondaires. En établissant le dosage, augmentez la dose régulière d’opioïdes d’environ 25%. Augmentez en même temps la dose efficace, en vous basant sur le critère de 10% de la dose quotidienne totale, administrée au besoin à chaque heure.
- Les effets des opioïdes varient d’une personne à l’autre. Envisagez de changer d’opioïdes si l’analgésie n’est pas suffisante ou si les effets secondaires sont intolérables malgré un bon dosage.