Pippa Hawley, B.Med., FRCPC

Methadone for pain in palliative care

Results from a survey of more than 800 BC family physicians indicate that most physicians already authorized to prescribe methadone for analgesic purposes support the requirement for authorization and believe the authorizing process is not burdensome.

ABSTRACT: Methadone is primarily a mu opioid receptor agonist with additional unique properties that make it a potent analgesic. Over the last 10 years this synthetic opioid has become one of the most important agents for treating opioid-nonresponsive pain in palliative care. Despite this, fewer than 1 in 10 medical practitioners in BC are authorized to prescribe methadone for analgesia. A survey conducted as a palliative care residency project (report in press, *Pain Research and Management*) found most physicians who are already authorized to prescribe methadone report experiencing little difficulty obtaining authorization through the College of Physicians and Surgeons of BC. In general these prescribers also support the requirement for authorization because of the need to avoid potentially serious drug interactions and overdoses. As well, survey results indicated that many physicians not authorized to prescribe methadone would be willing to apply for authorization in order to continue methadone prescriptions for a patient treated initially by a palliative care physician or pain specialist.

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Methadone is a synthetic opioid used for managing opioid dependence and as a second-line opioid analgesic. A dramatic increase in methadone use for pain has occurred over the last 10 years, with shared worldwide experience indicating that methadone has become one of the most important agents for treating opioid-nonresponsive pain in palliative care. Despite this, at the time of writing there were only 685 medical practitioners in BC authorized to prescribe methadone for analgesia (6.4% of registered physicians), with a significant proportion of these being pain or palliative care specialists. The paucity of family doctors able to take over care of methadone prescribing for stable patients is a barrier to methadone's use by palliative care and pain and symptom management teams, and limits our ability to allow anticipated natural deaths to occur at home, in hospice, and in residential care under the care of family physicians, rather than in acute care hospitals.

A recent survey of more than 800 BC family physicians explored the barriers to physicians obtaining the authorization to prescribe methadone for pain, with the goal of educating physicians through various initiatives, including articles such as this one. The survey, conducted by Dr Ryan Liebscher (resident in the Year of Added Competency in Palliative Care July 2009–June 2010, Division of Palliative Care, Department of Family Practice, Faculty of Medicine, UBC), was collected in summer and fall 2010 and analyzed in spring 2011. (Note that this article specifically addresses the use of methadone in palliative care and not the use of methadone in chronic noncancer pain. Physicians wishing to prescribe methadone for this purpose are advised to become familiar with the Canadian guideline for safe and effective use of opioids for noncancer pain.)

Role of methadone in palliative care

Though there are no large randomized controlled trials showing that methadone is superior to morphine or other opioids, small trials and studies using other methodologies have clearly shown that a switch to methadone

Dr Hawley is a general internal medicine and palliative medicine specialist, and is medical leader of the Pain and Symptom Management/Palliative Care Team at the Vancouver Centre of the BC Cancer Agency.

when other opioids are not tolerated or not effective is usually helpful, sometimes dramatically so.[1,2] Methadone solution is also extremely cheap, especially when compared with the long-acting preparations of hydromorphone, fentanyl, or oxycodone. Recent publicity about the epidemic of prescription drug abuse in Canada, especially of OxyContin, and the publishing of conservative Canadian consensus guidelines on opioid use in noncancer pain may have increased reluctance to prescribe opioids. However, physicians' lack of knowledge is the biggest barrier to good pain management for the many people living and dying with chronic pain.

Palliative care physicians or pain specialists often initiate and supervise trials of methadone for analgesia. After a successful trial, there may be no need for further close monitoring by a specialist, or the patient may move to another environment where a specialist is not routinely available. In these cases, the family physician becomes the most appropriate person to provide adequately spaced prescriptions as part of regular care of the patient, identifying any medical issues connected with methadone use and conferring with or referring back to the specialist if necessary.

Advantages of methadone analgesia

Methadone is primarily a mu opioid receptor agonist but also has the unique properties of delta opioid receptor agonism, N-methyl-D-aspartate (NMDA) antagonism, and serotonin and norepinephrine reuptake inhibition,[3] all of which contribute to its potency as an analgesic. Advantages of methadone include its high oral bioavailability, long duration of action, multimodal analgesic effect, lack of active metabolites, and safety in renal failure.[2] In addition, less constipation has been reported with methadone than with other opioids.

Methadone usually requires administration every 8 hours for pain, as opposed to once a day when used for prevention of drug withdrawal symptoms. The main container of the compounded liquid preparation must be kept refrigerated and safely out of reach of children, but individual doses can be carried safely for a day or more. Tablets are more convenient and less prone to measuring errors, but they are also more expensive and only covered by Pharmacare for patients registered with the BC Palliative Care Benefits Program.

Methadone has been widely found to be particularly useful for neuropathic pain, and may be administered orally, rectally, subcutaneously, or intravenously. Injectable methadone can be imported from the UK with Health Canada approval, but supplies are also available in most tertiary palliative care units, and can be transferred between pharmacies when required urgently. Injectable methadone can also be compounded locally for immediate use. For more information, see page 301, "Using methadone for pain: Practice points."

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Risks

Despite methadone's many advantages, and in common with other drugs, its use involves potentially serious risks.[4,5] Methadone has a long and variable half-life, which means accumulation and respiratory depression are possible if it is titrated up too rapidly. It also interacts with grapefruit and some drugs by way of multiple cytochrome P-450 pathways. At high doses, methadone has been reported to prolong the QT interval, though this is usually seen only in conjunction with other QT-prolonging drugs (e.g., some antidepressants and antipsychotics), or with other QT-prolonging conditions, such as hereditary syndromes or hypomagnesemia. When converting to methadone from another opioid the equianalgesic ratio is variable and the conversion process can be time-

consuming. Most problems with methadone occur within the first 4 weeks of therapy or after inadvertent coadministration with an interacting drug, most frequently ciprofloxacin. Additionally, caution is advised when administering methadone while stopping certain metabolism-inducing drugs such as carbamazepine.

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Authorization process

In Canada, the risks of methadone use are managed by a federal prescribing restriction. Exemptions from this restriction for analgesic purposes are obtained separately from the exemptions for addiction treatment, and the administration of these exemptions is delegated solely to provincial regulatory agencies such as the College of Physicians and Surgeons of British Columbia (CPSBC). In BC, authorization to prescribe methadone for opioid dependency requires an 8-hour course, followed by a preceptorship period and interview, plus registration of individual patients receiving methadone. By contrast, authorization to prescribe methadone for analgesic purposes is acquired by reading the CPSBC's "Recommendations for the Use of Methadone for Pain" and six selected articles, followed by a brief phone interview to confirm that key safety issues specific to methadone are well understood.[6] Registration of individual patients receiving methadone for pain relief has not been required for approximately 10 years, though many older physicians remember this being a requirement.

Most of the physicians we surveyed who were authorized by the CPSBC to prescribe methadone considered the authorization process effective and not overly difficult or burdensome. Physicians surveyed who had not previously considered becoming authorized had limited knowledge of the authorization process, but were willing to explore it if asked to do so.

Comments from respondents already authorized to prescribe indicated that most see a need for some mechanism to ensure prescribers are properly informed on the safe use of methadone in palliative care (e.g., "Use can be tricky—some training/experience necessary"). Comments also indicated almost all felt positive about the authorization process (e.g., "Very good organized process. The careful education [not onerous, given by a college registrar] was most helpful").

A small number of authorized prescribers disagreed, with one respondent condemning the process: "The exemption is a tragic piece of historical silliness and it creates great difficulties for patients and those few of us with an exemption… Get rid of the exemption please."

Only 20.5% of family physician respondents in a position to provide palliative care but not currently authorized to prescribe methadone recalled having had any training or education on methadone for analgesia. The number of these physicians who reported having received education about methadone for analgesia declined with age, dropping off after graduation from a high of 38% for those younger than 40 years, to 24% for those 40 to 50, to 18% for those 50 to 60, and to only 6% for those over 60. However, even looking at the younger age groups, these numbers are not sufficient to ensure equitable access to this important treatment modality.

Despite a variety of perceived barriers and misconceptions, over half of respondents not authorized to prescribe methadone stated that they would be somewhat or very likely to apply for an exemption to continue methadone prescriptions for a patient after treatment was initiated by a palliative care physician or pain specialist.

Conclusions

It was reassuring to find that survey respondents already authorized to prescribe methadone for analgesia reported that the process of obtaining authorization was easy, and that on the whole they were supportive of the requirement for authorization because of pharmacological concerns that pre-

scribers must be aware of to avoid inadvertent overdose. It was also reassuring to find that many respondents not authorized to prescribe methadone were willing to consider obtaining authorization so that their patients might benefit from this cost-effective agent for quality pain management.

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Competing interests

The author has received honoraria from Paladin Labs Inc., manufacturer of the methadone tablet Metadol, for speaking at medical education events about one of the company's other products, Abstral.

Using methadone for pain: Practice points

- To apply for an exemption from the federal restriction on methadone prescribing, contact the College of Physicians and Surgeons of BC at www.cpsbc.ca. State clearly that you are seeking authorization to prescribe methadone *for pain*. You will need to read "Recommendations for the Use of Methadone for Pain" (www.cpsbc.ca/files/u6/Methadone-Program-Recommendations-for-the-Use-of-Methadone-for-Pain-PUBLIC.pdf) and some references, and then have a brief telephone interview with a deputy registrar.
- Switching a patient to methadone from high doses of other opioids can be complicated and should be done only by physicians with sufficient knowledge and experience using methadone for pain, or in consultation with a palliative care physician.
- Methadone has a long and variable half-life: changes in dose can take more than 3 days to achieve full effect. Start low and go slow whenever possible.
- Methadone can interact with other drugs in potentially serious ways. When a patient is taking methadone for pain, check with a reliable pharmacological resource (e.g., as provided by the CPSBC), before stopping or starting any other medication.
- Methadone can cause prolongation of the QT interval and predispose to torsade de pointes. Check the patient's ECG if the dose of methadone is above 150 mg/day, or if the patient has any other conditions or is taking any other drugs that might also prolong the QT interval.
- Methadone doses should be reduced if liver function deteriorates, but do not have to be adjusted in cases of renal failure.
- When a patient becomes unable to take oral methadone, suppositories can be made up by a compounding pharmacy using the same dose as used for the oral route. Oral methadone liquid can also be administered rectally.
- Injectable methadone may be ordered in advance through Health Canada, and emergency supplies can be obtained from most tertiary palliative care units.

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