Methadone:
What is its Role in Cancer Pain Control?

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Mr. Henderson's situation

Mr. Henderson, 63, presented with a very large right upper lobe non-small cell lung cancer mass and extensive right pleural metastatic disease.

He had two pain syndromes:

- A somatic/visceral aching pain, reasonably well-localized to the right shoulder and right upper anteroaxillary thorax, was compatible with the known sites of tumours. He rated this pain at 6-7/10 at rest, on a pain scale of zero to 10 (0 = best, 10 = worst).
- A neuropathic right brachialplexopathy pain, compatible with plexus tumour invasion, and characterized by lancinating pain shooting down the right eighth cervical and first thoracic dermatomes, also rated 6-7/10 in pain at rest. There were associated paresthesias in the involved dermatomes, and paresis of the corresponding myotomes. Additionally, this pain had a severe incidental component (exacerbation with movement) rated at 10, such that Mr. Henderson could not use his right arm.

In the month preceeding palliative consultation:

- his OxyContin® (slow-release formulation) dose had tripled.
- he was using five to seven breakthrough doses of immediate release oxycodone per 24 hours.
- he was on gabapentin 1200 mg per 24 hours.

In this article:

1. **What are the indications for methadone use?**
2. **What are the advantages and disadvantages of methadone, compared to non-methadone opioids?**
3. **How do I rotate a patient safely to methadone from a non-methadone opioid?**

Why methadone?

Methadone is a synthetic opioid receptor agonist developed over 50 years ago. Its use subsequently declined after implications in numerous fatalities attributed to respiratory depression in inadvertent overdoses.[1,2] Over the last decade, however, interest in methadone's usefulness in cancer pain management has steadily risen. There are no randomized controlled trials to support the claim, but empirically, methadone appears to provide more effective analgesia with less risk of opioid neuropsychiatric toxicity than non-methadone opioids. It is particularly useful in cancer pain

syndromes requiring higher dose opioid therapy, such as neuropathic or incidental pain.

What is opioid neuropsychiatric toxicity?

This syndrome is secondary to the buildup of toxic metabolites, and is characterized by any combination of manifestations listed in Table 1.[3] Opioid neuropsychiatric toxicity can severely compromise pain control and patient quality of life. Methadone's lower incidence is clinically important.

What are the advantages of methadone?

There are several advantages concerning the use of methadone.

1. NMDA receptor antagonism

As well as being an opioid receptor agonist, methadone is an NMDA (N-methyl-D-aspartate) receptor antagonist.[5] The NMDA pathway is a major excitatory central nervous system (CNS) pathway involved in the neurobiology of pain.[6] Methadone's ability to dampen this pathway's excitation may explain its superior analgesic behaviour and, possibly, its lesser risk of opioid toxicity. These properties may also reduce the need for adjuvant analgesia, as Mr. Henderson's case (page 90) demonstrates. Methadone is now considered the opioid of choice in cancer pain syndromes requiring higher dose opioid therapy, such as neuropathic pain or incidental pain.[7] Its effective analgesic action in non-neuropathic cancer pain refractory to other opioid agonists has also been reported.[8-11]

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2. High oral/rectal bioavailability

Methadone has high oral bioavailability, and minimally lower rectal bioavailability.[12,13] Customized methadone suppositories (also administrable into colostomy sites) are simply and inexpensively made.[13] A suppository requires approximately 30 minutes for complete absorption (based on clinical experience).

3. Long half-life

This leads to a longer duration of action than other immediate-release opioids, characteristically between eight and 12 hours, offering the convenience of slow-release formulations.

4. Minimal dependence on renal elimination

In contrast to codeine, morphine, hydromorphone, oxycodone, and fentanyl (the only other opioids recommended for cancer pain control), methadone is minimally dependent on renal excretion (significant only when urinary pH is < 6).[14] Methadone may be the opioid of choice in the setting of significant renal impairment, a complication occurring in cancer patients, regardless of the involved

Table 1
Manifestations of opioid toxicity

Myoclonus
- progressing to grand mal seizures if unchecked

Delirium
- fluctuating cognitive impairment and level of consciousness
- changes in psychomotor behaviour (hypo- or hyperactivity)
- perceptual disturbances (nightmares, visual and/or tactile hallucinations)
- delusions (often paranoia)

Hyperalgesia
- loss of previous pain control; or
- severe generalized cutaneous allodynia

cancer pain syndrome. Methadone's primary route of elimination is hepatobiliary. Studies to date have implied safe use in conditions of hepatic impairment, but careful monitoring is advisable.[14]

Mr. Henderson's first assessment

Mr. Henderson was clearly experiencing opioid neuropsychiatric toxicity.

History revealed:

- drowsiness
- frequent myoclonus
- cognitive impairment
- the presence of tactile and visual hallucinations

Physical examination revealed:

- somnolence
- a Folstein Mini-Mental Status Examination score of 23/30 (expected norm for his age and level of education is 27/30)[4]
- dehydration
- myoclonic jerks ocurring every few minutes
- marked tenderness over the anteroposterior right shoulder and right upper anteroaxillary thorax
- no discernible right supraclavicular or axillary tumour but sensory and motor deficit evidence of a right brachialplexopathy
- severe right arm incidental pain

Given the severity of his toxicity, Mr. Henderson required immediate opioid rotation:

- He was switched to immediate release hydromorphone (slow-release opioid preparations should not be used in poorly controlled pain, due to the impossibility of rapid dose titration).
- Rehydration, to facilitate renal excretion of toxic metabolites, was accomplished with subcutaneous hydration.
- Intermittent antipsychotic use was necessary for 24 hours to control the hallucinations (Table 2).

Mr. Henderson's followup

By 48 hours the toxicity resolved and his pain control substantially improved. Within one week, however, both pains were again poorly controlled, with ratings and breakthrough analgesic use returning to original levels. Symptoms of opioid toxicity reappeared, although less severely than previously.

Due to the presence of severe neuropathic and incidental pain, and the recurring problem of opioid toxicity, the decision was made to rotate Mr. Henderson to oral methadone. This was done over three days. Gabapentin adjuvant analgesia was simultaneously discontinued.

By completion of the rotation to methadone, Mr. Henderson rated both pains at 0/10 at rest, and the incidental component at 3/10; an acceptable level for him. He regained limited use of his right arm. Over the remaining month of his life breakthrough analgesia was very rarely requested or deemed necessary by nursing staff, and there was no recurrence of opioid toxicity.

Table 2
Management of opioid toxicity

- Opioid rotation (decrease the new opioid equianalgesic dose by ~ 25%, due to incomplete cross-tolerance between opioids)
- Hydration (~1.5-2.0 L/24h)
- Short-term antipsychotic use, if clinically indicated (haloperidol 1 mg orally/subcutaneously every hour as needed)

Table 3
Management of opioid toxicity

Opioid	Oral	Subcutaneous
Codeine	100 mg	50 mg
Morphine	10 mg	5 mg
Hydromorphone	2 mg	1 mg
Oxycodone	5 mg	2.5 mg

Fentanyl transdermal: See manufacturer's chart
Fentanyl infusion: 10 mcg sc/24h ≈ 1 mg sc morphine/24 hour*
Methadone: 1 mg/24h ≈ 10 mg po methadone/24 hour*
* Only physicians experienced with these opioids should initiate their use.
Note: oral:parenteral ratio is 2:1

5. Low cost

Methadone is commercially available in liquid form. Most pharmacies, however, make solutions, capsules, or suppositories from less-costly methadone powder. Formulated in this way, methadone is up to 10 times less costly than equianalgesic doses of hydromorphone.[15]

6. Less constipating than non-methadone opioids

Like other opioids, methadone's side-effects include sedation, nausea, dry mouth, sweating, pruritus, and risk of urinary retention. Methadone, however, is less constipating than other opioids.[16]

What are the disadvantages of methadone compared to non-methadone opioids?

1. Methadone has wide and unpredictable interindividual variabililty in its half-life, causing unpredictable timing of respiratory depression risk on methadone therapy initiation.

Methadone's half-life ($T_{1/2}$), and correlated duration of action, varies between individuals, anywhere from six to 60 hours.[17] There is no laboratory test to determine a given patient's $T_{1/2}$. Given the general pharmacokinetic principle that administration of four doses of a drug, at appropriate intervals, is needed for stable serum level attainment,[18] stability of an individual's methadone serum level may occur anywhere from 24 hours ($T_{1/2}$ of six hours) to 240 hours ($T_{1/2}$ of 60 hours). During methadone initiation, the risk of respirato-

ry depression and its timing are unpredictable.[15] For this reason, in the author's setting, rotation to methadone from a non-methadone opioid is done over a minimum of three days in an institution (see Mr. Henderson's medication rotation). In the home, it is done over five to six days. These timelines allow for the development of tolerance to respiratory depression. Only physicians experienced in methadone use should initiate methadone therapy. Once the rotation is completed, however, the titration of methadone according to analgesic need is identical to non-methadone opioids.

In the home setting, careful assessment must ascertain the competence and reliability of the patient and significant others; if this is not the case, the rotation should be done in a controlled hospital setting.

2. Parenteral methadone is not tolerated subcutaneously.

The parenteral formulation of methadone available in North America is irritating to subcutaneous tissue, making this route of administration inadvisable.[19] Since long-term intravenous use is rarely considered practical in advanced cancer patients, methadone's parenteral administration is uncommon: hence the usefulness of methadone suppositories when the oral route is compromised.

3. Physicians must obtain a special licence to prescribe methadone.

Depending on the province, a special license must be obtained either from the Provincial College of Physicians and Surgeons, or directly from the Healthy Environments and Consumer Safety Branch of Health Canada. Obtaining the licence can take several weeks.

4. Not all pharmacies dispense methadone.

Prescribing physicians must familiarize themselves with dispensing pharmacies.

Mr. Henderson's medication rotation

Mr. Henderson was in hospital, permitting a three-day switch to methadone.

Over the three-day rotation, the non-methadone opioid dose is reduced each day by approximately one third of the original dose, and an equianalgesic dose of methadone is substituted.

Over a five-day rotation, the non-methadone opioid dose is reduced daily by one fifth of the original dose.

Daily clinician assessment and individual dose titrations, however, depending on analgesic and side-effect profiles, are strongly advised.

Mr. Henderson's rotation to methadone:

At the time of rotation Mr. Henderson was using 24 mg of oral hydromorphone (HM) every four hours, or 144 mg per 24 hours. His breakthrough pain analgesic dose was 12 mg orally every hour as required.

- 144 mg oral HM/24h ≈ 720 mg oral morphine/24h.
- 72 mg of methadone/24h, or 24 mg orally every eight hours, is the tentative methadone target end dose. For most patients an eight-hour administration interval is appropriate on initiation.

Day 1:

a) Decrease HM by ~ 33% (8 mg per dose), to 16 mg orally every four hours. The 48 mg (8 mg by six doses/24h) reduction in HM/24h ≈ 240 mg oral morphine/24h ≈ 24 mg oral methadone/24h.

b) Start methadone at 8 mg orally every eight hours.

c) Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 2:

a) Decrease each HM dose by another 8 mg, to 8 mg orally every four hours.

b) Increase each methadone dose to 16 mg every eight hours.

c) Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 3:

a) Discontinue HM.

b) Increase each methadone dose to 24 mg every eight hours.

c) Continue HM 12 mg orally every hour as needed for breakthrough pain.

Day 5:

a) Discontinue HM for breakthrough pain.

b) Start methadone 6 mg every hour as needed for breakthrough pain.

There are two accepted rules for calculating breakthrough doses:

1) 10% of the 24h total of regular doses.
2) Two hours worth of the 24h total of regular doses (slightly more conservative).

What are the equianalgesic dose ratios between methadone and non-methadone opioids?

This issue is crucial (Table 3). Many opioid equianalgesic conversion tables still portray methadone as equivalent to morphine in potency (1 mg of oral methadone equals 1 mg of oral morphine), and in duration of action (four hours), based on a 1967 study comparing single dose administration of both opioids.[20] In chronic dosing, methadone is five to 10 times more potent than morphine, and has a significantly longer duration of action.[12] Its initial extensive tissue distribution phase explains the discrepancy in duration of action between single and chronic dosing.[12] Use of the original equianalgesic ratio may lead to severe respiratory depression or death.

In the author's setting, the conversion ratio used is: 1 mg of oral methadone per 24 hours is approximately equal to 10 mg of oral morphine per 24 hours.[21,22] The conservatism of this ratio obviates the need to reduce the equianalgesic dose of methadone by 25% (Table 2). Even this revised equianalgesic ratio poses respiratory

depression risk if the patient is switched abruptly from a non-methadone opioid to methadone,[15] underpining the practice of the several day rotation protocol.

Are there other protocols for switching from a non-methodone opioid to methadone?

Other centres use other protocols, but this approach has proven clinically safe and effective.[15]

Should methadone be a first or only higher line opioid of choice?

Initially the author's center viewed methadone as a third or even forth line opioid, to be used when sequential trials of high dose non-methadone therapy did not achieve pain control or caused opioid toxicity. With increased experience over the last decade the practice is shifting to immediate methadone initiation if the cancer pain syndrome is known to require high dose opioid therapy, or in patients with renal impairment. De Conno et al[23] have experience using methadone as the first line opioid in cancer pain control, initiated in opioid-naïve patients or patients switched "cold turkey" from low dose non-methadone therapy. They reported no cases of respiratory depression in 196 patients whose stable mean daily dose was 24 mg +/- 25 mg. Equianalgesic ratios appear to vary, depending on non-methadone doses at the time of methadone initiation,[21] with the lower methadone:morphine ratio of 1:5, rather than 1:10, at low dose opioid therapy. CME

Take-home message

- Methadone is the opioid of choice for neuropathic and incidental cancer pain.
- Methadone is the opioid of choice for patients with renal impairment.
- Methadone is five to 10 times more potent than initially described.
- There is a risk of respiratory depression on methadone initiation.
- Only experienced physicians should initiate methadone therapy, but subsequent titration is identical to non-methadone opioid therapy.
- Methadone is inexpensive.

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Net Readings

1. Cancer Page.Com: www.cancerpage.com/cancernews/cancernews3500.htm
2. American Society of Clinical Oncology: www.asco.org
3. University of Alberta, Division of Palliative Care Medicine: www.palliative.org

See page 21 for Frequently Asked Questions on methadone and cancer.