Special Review

When to Use Methadone for pain: A Case-Based Approach

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Abstract

The case studies are written in this article to illustrate how methadone might be used for pain in the Indian context. These cases might be used for discussion in a multidisciplinary team, or for individual study. It is important to understand that pain requires a multidisciplinary approach as opioids will assist only with physical, i.e. neuropathic and nociceptive pain, but not emotional, spiritual, or relational pain or the pain of immobility. The social determinants of pain were included to demonstrate how emotional, relational, and psychological dimensions of pain amplify the physical aspects of pain. The case studies follow a practical step-wise approach to pain while undergoing cancer treatment, pain toward the end-of-life and needing longer acting opioid. Methadone in children, and methadone in conditions of opioid toxicity or where there is a need for absorption in the proximal intestine cases are included.

Keywords: Cancer treatment, children, end-of-life care, long-acting opioid, methadone, multidisciplinary approach, small intestinal absorption

Introduction

The recently reformed drug policy by the Government of India, methadone was introduced as one of the Essential Narcotic Drugs(END) for pain management. Methadone is more economical and efficient than other opioids as the product has two racemic mixtures and can manage neuropathic pain better. However, methadone if used inappropriately can cause death due to adverse effects. This article will assist a physician, in the form of a case based approach and manage pain safely to achieve goals and less harm to an individual patient. The name of individual patient has been altered to protect identity, privacy and confidentiality. A case based approach is relevant to Indian context and may be helpful when used appropriately in other developing countries, who may wish to obtain methadone as a level 3 World Health Organization ladder opioid. Individual cases are presented with the history, physical, care plan and a discussion to engage physicians and allied health professionals to collaborate and achieve good pain management in a patient.

Case 1: Cancer Treatment-Related Pain That Resolves

Rathode is a 54-year-old laborer diagnosed 4 months ago with squamous cell cancer of the tongue. He has finished 30 fractions of radiation with concurrent chemotherapy. The intent of the therapy was curative. After the chemoradiation, he started losing weight with reduced intake due to painful swallowing. He agreed to a nasogastric tube for 2 weeks, which has now been removed. He describes his pain as shooting and burning. He still cannot swallow because the pain continues to be severe. The current medication helps to reduce the pain slightly. His wife mentioned sudden jerky movements of his leg when he is resting.

He gave a history of tobacco chewing for the past 30 years. He does not drink alcohol. He has not been able to return to work. He is constipated and complains of dry mouth. The review of other systems is unremarkable except for low mood and worry about his return to work.

His current medications are 15 mg morphine 4 hourly during the day and 30 mg at night before bed. He takes paracetamol 650 mg every 6 h as well. He is also on a weaning dose of dexamethasone, currently at 8 mg once a day, and amitriptyline

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50 mg at night. Social history: He was a daily wages worker. For the past 4 months, he was unable to go to work due to his physical concerns. His wife is now forced to work as a housemaid due to their financial constraints. Their son who was studying at the local polytechnic college dropped out and started on a job recently in a nearby shop. Rathode is upset that his son left his studies to bring income for the family. He also worries about his wife working.

His daughter is a nurse at a local clinic. She had married against the wishes of the family and lives in the neighborhood with her husband. Her marriage was an emotional trauma to the family. His physical examination is remarkable for:

- Pupils are 1 mm and reactive
- Inability to open his mouth more than 4 cm
- No thrush on his palate
- Radiation changes over the skin of the right side of the neck and cheek
- Decreased mobility of neck in flexion, extension and lateral turns
- The abdomen has hypoactive bowel sounds.

Discussion

The suffering of this patient is likely arising from the many contributors to pain. Besides the physical injury to his head and neck muscles and parts of the neural system by the radiation, he is unable to perform basic functions of living. He cannot eat and is constipated. He is also emotionally devastated. His personhood has been affected, with an inability to provide for his family. No one therapy or intervention will solve all of Rathode's pain.

Intervene step by step:

1. Initial steps to focus on areas most important to the patient. Reassure Rathode that we will be working together to alleviate his suffering from pain – described below
2. Resolve constipation by optimizing stimulant/lubricant laxatives
3. Provide inputs from a therapist with skills in speech/swallow rehabilitation exercises. This can assist this patient to improve mobility of the jaw and neck muscles
4. Encourage compliance with medications and exercises through a network of community volunteers to motivate and support the patient at home
5. Role for social worker and the team: may identify and connect the community resources for supporting the family during this crisis period
6. When adequate rapport is built, a family meeting to acknowledge and openly discuss the disturbed family dynamics may be helpful. The aim would be reframing understanding of the situation, surfacing affections for each other and healing the disturbed relationships. The daughter who is a nurse can be a valuable and competent caregiver at home.

Reviewing Rathode's analgesic regime, it was agreed that morphine is causing adverse effects with inadequate improvement in pain. The patient's pain goals were reassessed and documented for monitoring relief.

Can we consider methadone for this patient?

The pain has a strong neuropathic component to it and he is getting minimal relief from morphine and other drugs. The pain is affecting functions of daily living–swallowing, speech and sleep. Since he is at the clinic, a baseline electrocardiogram (ECG), magnesium, and potassium can be ordered, before starting methadone. Methadone has been shown to be superior than fentanyl in head-and-neck cancer.[1]

How might we initiate methadone therapy at this stage?

We may use one of the methods listed below:

a. Start low and go-slow method: methadone 2.5 mg every 8 h.[2] Take morphine 10–15 mg 4 hourly as needed. Take paracetamol and amitriptyline as before. Continue weaning the dexamethasone as planned
b. Nighttime dose method: start with 2.5 mg at night and check impact on pain relief[3]
c. Converting total daily morphine to methadone: 15 mg × 6 = 90 mg is the morphine daily dose (MDD). 90 mg/4 = 22 mg methadone a day. The dose for methadone would be 7.5 mg every 8 h.[4]

The physician caring for the patient decided on the dose methadone 2.5 mg every 8 h. The family was explained the regime and his daughter was also involved in his care, which made her feel accepted back into the family. He was also given instructions for breakthrough medication: morphine 15 mg as needed not earlier than 4 hourly and to a maximum dose of 90 mg/day.

d. Instructions given to the family when starting methadone were:
    i. Keep it safe in a tightly closed container. Keep away from the reach of children
    ii. Use this solution in the prescribed manner. Shake the solution before use
    iii. This medicine has been prescribed only for that patient's use. Do not share with any other person
    iv. Do not start any new medications without consulting the PC clinic
    v. Report to the clinic if there are palpitations, too much sleepiness, dizziness, nausea, vomiting, or any other new complaint or unusual behavior.

di. The palliative care team called the patient for the next 2 days to check his overall response to the regime, his pain relief, resolution of constipation, and to clarify any questions that the patient or his family had

dii. The following week, the patient was eating more easily. His wife reported that he did his oral and neck exercises more easily as well.

The family dynamics became more cohesive with the multimodal interventions. In 2 months – his son was back to the polytechnical college with support from the community and a part-time job at the shop. The whole family was looking forward

joyfully to the daughter's first child. Rathode's pain is acceptably controlled, although not fully resolved. He is able to have kanji, soups, and soft fruits like banana. He gets 5-6 hours of sleep.

In 4 months, the patient had started to forget the midday methadone, and it was tapered gradually under the team's supervision. The doctor ensured that he had no leftover methadone that could be mistakenly taken by a child or another family member. He continued on the amitriptyline at night. He continued to be monitored by the oncology team every 4 months, for recurrence of his cancer.

Case 2: Pain Toward the End-of-Life

Sandhya is a 65-year-old woman with advanced cervical cancer. She is not able to get out of bed. She has an aching pain in her low back. She also experiences severe pain in her pelvic bone that shoots to her legs. She stifles her moaning when her grandchildren are home from school. She is not short of breath. She has regular bowel movements.

The palliative care home team have recently increased her morphine with instructions to take it as 15 mg 4 hourly. Her family notices that this medication sedates the patient but does not seem to help with the pain. Her family feeds her at regular intervals during the meal times, with great difficulty. In addition, the three women in the family have to take turns staying awake with her all night because she gets restless and tends to fall out of bed.

Her current medications are:
- Morphine 10 mg 4 hourly
- Bisacodyl 10 mg twice daily
- Pregabalin 75 mg twice a day.

Social history

She worked as a tailor. Even after the diagnosis, she continued working. She was apparently well until 5 months ago. Her husband was a fisherman who abandoned them 35 years ago. She lives with her daughter Asha and her family. Sandhya's younger two sisters, Daya and Geeta, have come to help. She and her close family have full insight about the extent of her disease. Besides pain, she finds feeding to be a burden.

Physical examination is remarkable for:
- Easily awakened, but then moans
- Cachexia
- Dry mouth
- Pupils are pinpoint
- Occasional jerking on the arms.

Discussion

Sandhya is suffering, with every wakeful moment full of pain. Her beloved sisters are ready to do anything to help, but the physical pain is so excruciating that it brings tears to their eyes. The pain appears to be mixed type-nociceptive at the low back and neuropathic pain as the shooting pain that travels down her left leg. She is delirious at night.

She also appears to be experiencing opioid toxicity suggested by the myoclonus, pinpoint pupils, and sedation. In this setting, the best treatment option is opioid rotation, which is switching from one opioid to another to improve the analgesic response and to reduce side effects.[5]

How do we approach care for Sandhya?
1. Reassure the patient and the family that we are taking measures to make her feel better
2. Acknowledge their efforts, yet gently explain to the family regarding her reducing feeding requirements, and how force feeding is distressful to Sandhya and a burden to her biological system. Help them with a list of nutritious soft feeds, that may be easily made in their kitchen and be offered to Sandhya in small quantities as acceptable to her
3. Consider steroids, for example, dexamethasone 8 mg daily as an anti-inflammatory as it can stimulate appetite and combat cancer-related fatigue.[6]

Is she a candidate for methadone? What are the considerations here?
a. There is neuropathic component to her pain
b. She has inadequate pain relief with escalating dose of morphine
c. She is opioid toxic
d. She appears to have attentive caregivers.

Before starting methadone in this setting, it may not be necessary to get the baseline investigations and ECG as the patient is close to the end-of-life.

How may we start methadone for Sandhya?
1. Withhold the ongoing morphine regime
2. Start low and go-slow method: methadone 2.5 mg every 8 h with lower dose of morphine 5 mg every 2–4 h as needed[2]
3. OR-Night time dose methadone: start with 2.5 mg at night and see how it helps. This is NOT a good option for Sandhya, as she has signs of opioid toxicity
4. Convert morphine to methadone: 10 mg × 6 = 60 mg is the MDD 60 mg/4 = 15 mg methadone a day. The 8 hourly dose of methadone then will be 5 mg. Morphine 10 mg will continue as the breakthrough dose.[4]

The physician caring for the patient decided to give a prescription for methadone 2.5 mg every 8 h for the 1st week. In addition, she received dexamethasone 8 mg in the mornings. After the 1st week, she was alert and lying down comfortably during the day without moaning or crying. She had not needed any breakthrough pain medication. The dexamethasone was slowly tapered to 4 mgs and stabilized at that dose.

In subsequent weeks, her general condition worsened and she stopped eating. As she was unable to swallow medicines, a liquid slurry was made with the methadone and put into her cheek for continued pain relief.[7] She continued to receive general nursing care for her skin, mouth, and perineum. She passed away peacefully and symptom-free, with her two sisters and daughter at her side.

Case 3: Pain Needing Longer Acting Opioid

Paresh is a 25-year-old man with an advanced osteosarcoma. He was diagnosed when he was 20 years old and underwent an above the knee amputation of the right leg. He did well until 3 months ago when he had a recurrence in his lungs. He is bothered by night time pain in his legs and chest. If he forgets a dose of morphine, he notices that he has a dull pain in the chest.

Social history

He manages a shop out of his home, and his wife works at a local hospital as a health aide. He has two children studying in school. He does not smoke or drink alcohol.

He takes morphine 10 mg every 4 h during the day with good results but cannot sleep at night due to pinching, shooting pain in his right stump that starts at 2 am. He has tried increasing his night time dose of morphine and it has not helped.

His physical examination is remarkable for:

- Walking with crutches
- Stump is well healed and without erythema
- Lung examination is without wheezes.

Discussion

Paresh appears to be managing well except at night. He suffers pain in the middle of the night that disturbs his sleep and triggers anxiety. The pain is neuropathic and nociceptive in nature. Increasing dose of morphine at bed time has not helped him.

Is he an appropriate candidate for methadone?

A. He might do well at night, if put on methadone just at night, due to the longer acting nature of methadone.
B. His treating physician started methadone 2.5 mg just at night and not during the day. Paresh now notices that he is no longer in pain at night and when he wakes up in the morning. He is energetic enough to prepare the children for school.
C. Later, as his disease progresses, his regime of methadone is changed to 2.5 mg every 8 h. He is also advised to take morphine 10 mg not more than every 4 h if required for breakthrough pain..

Case 4: Poorly Controlled Neuropathic Pain in a Child

Rudra is a 13-year-old boy (weight 30 kg) with advanced Ewings Sarcoma diagnosed 1 year ago. At the time of diagnosis, he already had a large mass in the right proximal humerus and lung metastases. He complains of severe pain, score 7–8/10, radiating down to right upper limb, associated with tingling and numbness. He cannot sleep at night, due to pain and shortness of breath. He moans loudly, keeping others awake. He has lost 5 kg because he has no appetite and refuses to eat. He is having a bowel movement every other day. His mother reports occasional irrelevant speech. He and his family are sleep-deprived.

He is the youngest of the three siblings. His parents are farmers but now have no steady source of income. His older brothers dropped out of school to earn daily wages for the family. His family is closely knit, but Rudra feels guilty that his family is undergoing hardship due to him. He misses school. He refuses to meet with his school friends. He hates and fears hospitals. He has lost hope that the pain will ever improve. He is on morphine 10 mg Q4 h, Imipramine 25 mg HS, Bisacodyl 10 mg HS. In the past 24 h, mother gave him 3 rescue doses of morphine 10 mg.

His physical examination is remarkable for:

- Drowsy, irritable
- No eye contact. Appears withdrawn and angry
- Right humerus mass is tight, warm, and heavy.

He does not have free range of movement of the right shoulder due to the mass,

Discussion

Rudra appears to have contributors to pain-at physical, emotional, and spiritual levels. The pain is both neuropathic and nociceptive. Methadone has been demonstrated as safe in children with cancer[8] and with neurologic impairment (Hauer, 2014).[9,10]

Step by step:

1. His MDD is 80 mg– including the rescue doses.
    a. Using the equianalgesic table for methadone, this is equivalent to 80/4 or 20 mg or 5 mg in the morning and afternoon and 7.5 mg at night
    b. Using the start slow and go-slow method, we would start methadone 2.5 mg every 8 h and slowly titrate up every 5–7 days.

The palliative care physician decided to start methadone 2.5 mg in the morning and at 2 PM and 5 mg at night for the first week. Rudra and his mother were also advised to take the morphine 10 mg as needed for breakthrough pain. He had a better night sleep almost right away, which was a blessing for the sleep-deprived family. He continued to need the breakthrough morphine 4 times a day, and some more with activity.

Over 2 weeks, the palliative care team increased his dosage to 5 mg in the morning and at 2PM with 10 mg at HS. On this regimen, he needed morphine about once a day. He was alert and able to interact with family throughout the day.

The palliative care social worker helped the family get funds from local volunteer groups and government schemes. Rudra's older siblings were able to return to school and only work after school. Rudra was counseled and reconnected with his best friend from school. The palliative care team helped Rudra go to school with his best friend and visit his favorite teacher.

Case 5: Allodynia and Opioid Toxicity

Prashant, a 67-year-old retired bank manager, who was diagnosed to have multiple myeloma in July of 2014. He has

multiple lytic lesions involving axial and appendicular skeleton along with a sternal plasmacytoma. He did have autologous stem cell transplantation in November 2014, following chemotherapy. He is on lenalidomide therapy. He required radiation therapy to cervical spine in October 2015 for neck pain.

He showed a positive response to an oral morphine trial and was titrated to a dose of 30 mg 4 hourly, with breakthrough pain medication morphine 5–10 mg hourly if needed. He also takes paracetamol 650 mg 3 times a day. He is using 5–6 breakthrough morphine in a day. When his dose exceeded 20 mg 4 hourly, he developed hallucinations. With subsequent increases in dose, he developed myoclonus. Pain has increased despite the increasing doses in the sacroiliac joints (10/10) and left side of sternum (5/10). The pain descriptors include sharp, deep, twisting pain the sacral area, and burning with frozen feeling in the sternal area. In the sternal areal, he also notices pins and needles periodically, especially when he is active. His bowels are working while on laxatives.

For the past 3 days, his bed sheets have increased his reports of pain "all over". He feels uncomfortable when his wife tries to touch or massage his back.

He has difficulty with activities of daily living, poor sleep and his mood is low.

Social history: His wife and two adult sons are very supportive. Nonsmoker and does not drink alcohol and no financial issues.

Clinically, he is able to stand and walk to the toilet with pain in the SI joint area. He has a mass which has reduced on the left side of the sternum near 2 and 3rd rib area. His pupils are <1 mm and reactive. He feels pain in the sternal area when he is moving in bed or sitting up.

Discussion

Pain and poor night time sleep had bothered him but recently the jerky movements and bad dreams have upset him more. He spilled a coffee cup in his hands yesterday all over himself and on the table. He is able to eat soft food but his taste is poor and he has nausea. As the dose of morphine increased, his pain escalated and signs of neurotoxicity worsened, causing alarm for him and his family.

He has likely developed opioid-induced hyperalgesia (OIH), in addition to opioid toxicity. He requires an opioid switch/rotation.[11]

How to manage step by step the present state:

1. Pain management to reduce his distress, along with restful sleep and better mood are the goals
2. Evidence shows that use of methadone along with morphine or opioid switch to methadone can reduce the toxicity and hyperalgesia
3. His present dose of morphine is 220 mg in 24 h.

The safe option to reduce his distress; start low and go-slow method:

He is reporting pain of 10/10 in the sacral area and 6/10 in the sternal area at present.

1. To reduce opioid toxicity hydration is a good approach with normal saline 1-2 litres in 12–24 h., if possible intravenously
2. Adding methadone 2.5 mg or 5 mg three times a day on the 1st day. A total of 2.5 mg three times a day was chosen for Prashant
3. Morphine was reduced to 20 mg 4 hourly but breakthrough morphine was continued at 5–10 mg hourly if needed
4. At the end of 48 h, he felt he was sleeping better and myoclonus was less
5. On the 5th day, the dose of methadone was increased to 5 mg three times a day and morphine scheduled dose was stopped. He used 3 breakthrough morphine 5 mg doses in 24 h
6. On the 10th day, the dose of methadone was increased to 7.5 mg three times a day and morphine breakthrough medication was withdrawn. He was agreeable to take paracetamol 650 mg if needed 3 hourly was ordered but he did not use it. His morphine daily dose (MDD) is 220mg. His methadone dose is calculated to be 27 mg in 24 hours.

Patient at the end of titration required 7.5 mg (1.5 tablets of 5 mg) 8 hourly with good relief of pain, restful sleep at night, being sharp in the day with no myoclonus or delirium. He is not on any other opioids, nonsteroidal anti-inflammatory agents or breakthrough medication. His pain was manageable and reported 2/10 but no burning, pins and needles or sharp pain. Dull ache persisted which he could tolerate.

Case 6: Need for Absorption in the Proximal Intestine

Ganesh is a 42-year-old with adenocarcinoma of the lower rectum with polyps in the transverse and descending colon, for which he required a total colectomy including anus and ileostomy. Postoperatively, he required chemotherapy and received six cycles. Following chemotherapy, due to neutropenia and sepsis, he required intensive care unit admission and intravenous antibiotics. Following this episode, he developed peripheral sensory neuropathy and pain in the perineum-proctodynia.

Initially, he was given meperidine by the surgical team which led to nausea and vomiting and was changed to morphine. At the time of palliative care involvement, he was using 20 mg of morphine every 4 h and morphine 10 mg four or five times day for breakthrough pain. He was reporting 8/10 pain in the perineum which was a sharp pain, especially when he was using his perineal muscles to urinate. It was a spasmodic sudden, sharp pain and lasted 8–10 min. His sensory neuropathy pain was equally distressing as persistent and continuous pain with pain descriptors of pins and needles, walking on his feet was like walking on pebbles with poor balance.

Ganesh was very distressed with his pain. Morphine was not helping to reduce pain, his night time sleep was poor and he

was getting depressed but with no suicidal ideation. He had an earlier ECG and the QT/QTc was under 450 msec. His blood work including electrolytes were normal.

His ileostomy output was around 2–3 litres a day requiring hydration periodically. He also noticed pieces of tablets and occasionally full tablet in his ileostomy bag when he was emptying it.

After discussion with him and his wife, he agreed to try liquid morphine. His MDD was 160–170 mg in 24 h. Tolerance and fragments of morphine may be in the ileostomy bag due to short gut was discussed. Despite using liquid morphine 30 mg 4 hourly, his pain did not improve. The dose was increased gradually to liquid morphine 50 mg 4 hourly. He did see minor benefit in his sharp pain but little change in "pins and needles" type of pain.

Ganesh and his wife agreed to a therapeutic trial with liquid methadone. According to the MDD of 350 mg and methadone ratios 1:8, his requirement of methadone was 30 mg in 24 h.

Since some particles of medication collected in the ileostomy bag, it was hard to calculate his true need to control pain.

He was allowed to stay on morphine 50 mg 4 hourly with 10 mg 2 hourly breakthrough and liquid methadone 1 mg three times a day was added. Two days later, he reported reduction in the intensity "pins and needles" pain and scheduled morphine dose was reduced to 30 mg 4 hourly. At the end of 5 days, liquid methadone was increased to 2 mg three times a day. He noticed improvement in the sharp pain in the perineum. At the end of 22 days, his liquid methadone dose was titrated to 5 mg three times a day. He had stopped the use of scheduled and breakthrough morphine.

Discussion

Conventional opioids have little or no influence on N-methyl-D-aspartate receptors. In patients with shortened intestines, ("short gut"), fragments or the entire pill may be seen in the contents of the ileostomy or colostomy bag or in stools. Liquid methadone seems to be absorbed almost completely by the time it reaches jejunum, which serves as an advantage in addition to its efficacy in neuropathic pain.

To convert the MDD 360 mg, a ratio of 1:12 is used -30 mg of methadone in 24 h. However, there is great variability: for Ganesh, the requirement to reach a manageable pain level was methadone 15 mg in 24 h. For this reason, it is frequently better to "start low and go-slow."

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Conflicts of interest

There are no conflicts of interest.

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