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Original Article

Chart Review and Practical Recommendations for the Use of Methadone as an Alternative to Opioid Rotation in the Management of Cancer-Related Pain

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Abstract

Introduction Palliative care, with a focus on enhancing the quality of life for individuals facing life-limiting illnesses, relies on effective pain management as a fundamental component. Opioids, particularly methadone, play a crucial role in addressing moderate to severe pain in palliative care due to their unique pharmacological properties. Methadone, a long-acting opioid agonist and N-methyl-D-aspartate receptor antagonist, is valuable for treating both nociceptive and neuropathic pain. However, the transition to methadone from other opioids requires careful consideration.

Objectives This study examines the use of methadone as an alternative to morphine or fentanyl for managing refractory cancer pain in a tertiary care hospital in India.

Methods We conducted a retrospective analysis of anonymized medical records of cancer patients initiated on oral methadone for pain management at a tertiary cancer center's palliative medicine outpatient clinic from February 2020 to June 2021. Data included demographic characteristics, pain descriptions, concurrent analgesic use, reasons for transitioning to methadone, rotation methods, methadone dosages, clinical outcomes, adverse effects, and treatment discontinuations. Patients were routinely followed up, with pain scores, morphine equivalent daily doses, and methadone requirements recorded at each visit.

Results Forty-four patients received methadone, either as a coanalgesic (41/44) or primary opioid (3/44). Refractory cancer pain, with a neuropathic component, was the predominant indication for methadone use. Following the methadone initiation, all patients experienced significant pain relief. Median daily methadone dose increased from 5 to 7.5 mg after 1 week. Adverse effects were minimal, with one patient experiencing QTc interval prolongation. Patient-specific factors often necessitated deviations from equianalgesic conversion tables in determining methadone dosages.

Conclusion Methadone offers a viable option for refractory cancer pain when conventional treatments fall short. Physicians should prioritize personalized titration

Keywords
- methadone
- cancer pain
- opioid rotation
- equianalgesic conversion
- pain relief
- side effects

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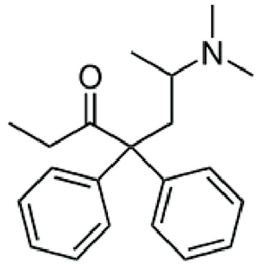
and thorough assessment during opioid rotation, rather than relying solely on conversion tables. Further research is needed to explore alternative approaches for opioid rotation and to expand our understanding of methadone's optimal use in cancer pain management.

Introduction

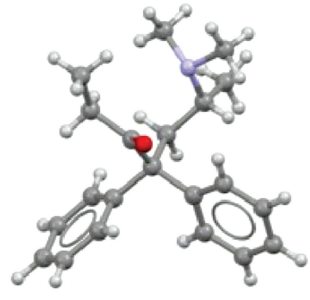
Palliative care aims to enhance the quality of life for individuals facing life-limiting illnesses, focusing on the relief of suffering and the provision of physical, psychosocial, and spiritual support. Effective pain management lies at the core of palliative care.[1] Opioids have long been the mainstay of analgesic therapy in palliative care, providing effective pain relief for patients with moderate to severe pain. Among the opioids used, methadone has emerged as a distinctive and increasingly utilized option. Originally developed as a long-acting analgesic and an alternative to morphine for chronic pain management, methadone's unique pharmacological properties make it an asset in the palliative care setting.[2]

As a long-acting opioid agonist and N-methyl-D-aspartate (NMDA) receptor antagonist, methadone is useful for treating both nociceptive and neuropathic pain. It is a racemic combination of R and S enantiomers, with R being 8 to 50 times more powerful than the S enantiomer[3] (►**Fig. 1**). Methadone's mechanism of action involves blocking the reuptake of serotonin and norepinephrine, as well as binding noncompetitively to NMDA receptors. Furthermore, methadone interacts with opioid receptors, specifically the mu, kappa, and delta subtypes.[3] Its distinct mode of action is thought to be what reduces the potential tolerance that can arise with long-term opioid pain management. Patients with renal and hepatic impairment, who have few options left for opiates, benefit the most from methadone. Rotations to methadone are complex. Various methods can be employed to transition to methadone, including rapid conversion or the stop-and-go approach (which entails ceasing the initial opioid and switching to methadone at an equianalgesic dosage), cross tapering, the 3-day switch (which involves gradually reducing the current opioid dosage while progressively increasing the daily methadone dose over a 3-day period) and ad libitum (wherein patients self-adjust their methadone dosage using pro re nata). However, no evidence suggests that any of these methods is more efficacious than the others.[2,4,5]

In India, methadone was first made available in 2012 as a substitute therapy drug to treat opioid addiction. In 2014, it was made available commercially for the treatment of pain.[6] In 2017, oral methadone was added to the 20th edition of the World Health Organization's standard list of essential medications.[7] Methadone proves highly effective in the treatment of complex pain syndromes often seen in India's prevalent types of cancer, such as head and neck, genitourinary, breast, and gastrointestinal cancers. These pain syndromes involve a combination of nociceptive and neuropathic pain.[8] In clinical practice, when considering the appropriate choice among methadone, morphine, fentanyl, buprenorphine, tapentadol, and tramadol for managing cancer pain, it is imperative to adopt a comprehensive and



Methadone: Skeletal formula



Methadone: Ball–and–stick model based on the crystal structure

Fig. 1 Methadone chemical formula. (Adapted from: PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. PubChem Compound Summary for CID 4095, Methadone [cited August 28, 2023]. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Methadone.)

evidence-based approach. These analgesic agents possess varying pharmacological profiles, efficacy, and potential adverse effects. The selection of the most suitable option should be guided by the principles of personalized medicine, considering patient-specific factors and the nature of the pain being addressed.[9] Methadone, an opioid with NMDA receptor antagonist properties, can be considered when there is neuropathic pain or opioid resistance. However, careful dose titration and monitoring of electrocardiogram parameters, especially the QT interval, are crucial due to the potential for QT prolongation and torsades de pointes (TdP) (distinctive form of polymorphic ventricular tachycardia).[4] Morphine, a classic opioid, remains a cornerstone for cancer pain management. Its wide range of formulations (immediate-release, extended-release, and intravenous) allows tailoring of treatment to the patient's pain pattern. The equianalgesic conversions between opioids should be followed meticulously to ensure a smooth transition.[10] Fentanyl, available in various delivery forms (transdermal patches, buccal lozenges, and parenteral formulations), is advantageous for patients who have difficulty with oral medications such as in head–neck cancers or require rapid onset of action (intravenous route). Dose titration is essential to avoid overdosing when switching to or from fentanyl due to its potent nature.[11] Buprenorphine, a partial mu-opioid receptor agonist, can be considered for patients with a history of substance abuse or for those needing long-term pain management. Its ceiling effect on respiratory depression contributes to its relative safety, although its efficacy in severe cancer pain might be limited.[12] Tapentadol could be considered for moderate to severe pain with neuropathic components. It combines mu-opioid agonism with norepinephrine reuptake inhibition. Side effects include potential for serotonin syndrome in combination with serotonergic medications.[13] Tramadol, an atypical opioid, has both mu-opioid receptor agonism and serotonin–norepinephrine reuptake inhibition. It can be useful in mild to moderate cancer pain with a neuropathic component. Caution is advised in patients with a predisposition to seizures, as tramadol lowers the seizure threshold.[14]

In all cases, an individualized approach should be followed, considering factors such as the patient's pain intensity, previous opioid exposure, comorbidities, concurrent medications, and potential drug interactions. Regular assessment of pain relief and monitoring for adverse effects are pivotal. Multidisciplinary collaboration involving pain specialists, oncologists, pharmacists, and palliative care experts can further optimize pain management strategies (►**Supplementary Materials 1** and **2**). Cost can be a guiding factor while choosing pain medications, especially in settings where patients must pay out of pocket.[15] For a weeks' supply, fentanyl is available as expensive transdermal patches (for fentanyl 25 µg transdermal patch [one patch lasts for 3 days]: INR 1000 – INR 2000 compared with INR 150 – INR 300 for equianalgesic dose of morphine, INR 600 – INR 1000 for buprenorphine patch [one patch lasts for 7 days], INR 400 – INR 600 for tapentadol, and INR 200 – INR 300 for tramadol). Methadone, on the other hand, is cheap (INR 150 – INR 200 for equianalgesic dose of methadone supply for a week) and a suitable alternative for opioid rotation in refractory cases.[16]

The primary goal of this study is to provide a review of our experience using methadone as either a coanalgesic or primary option for cancer pain management. Additionally, we aim to increase awareness about the use of opioids, particularly methadone, for cancer pain relief.

Methods

We conducted a retrospective analysis of the anonymized medical records of cancer patients who were initiated on oral methadone for pain management at the palliative medicine outpatient clinic in a tertiary cancer center. The review encompassed the period from February 2020 to June 2021. The data extracted from patients' medical records encompass various aspects, including demographic characteristics, diagnosis, comprehensive pain description (including type, severity, and baseline morphine equivalent daily doses [MEDD]), concurrent usage of other analgesics, rationale for transitioning to methadone, approach employed for rotation, ultimate and anticipated methadone dosage, clinical outcomes related to pain management, any observed adverse effects, and information pertaining to the withholding or discontinuation of methadone treatment. These patients were routinely followed up at 1-, 2-, and 4-week intervals after starting methadone, and the pain scores, MEDD, and methadone requirements were charted at each follow-up.

Results

Between February 2020 and June 2021, 44 patients received methadone as a coanalgesic (41/44) or primary opioid (3/44) (►**Table 1**). Among the participants, 24 individuals experienced a combination of somatic nociceptive and neuropathic pain, while 15 individuals reported a mixture of visceral nociceptive and neuropathic pain. Additionally, three participants exclusively had somatic nociceptive pain, and two patients specifically reported neuropathic pain. Refractory cancer pain not responding to "standard" treatments was the indication for methadone for 41 patients, the rest had a deranged liver function and one deranged renal function. Before methadone, the median numeric rating scale pain score was 8 (severe), standard deviation (SD) 1.4, with 53.49% MEDD ranging from 60 to 120 mg (median: 120 mg, SD: 74.9 mg). Forty-one had undergone rotation to methadone as a coanalgesic with a nonmethadone opioid, while three were solely on methadone. All patients received adjuvant analgesics as needed. The method used for opioid conversion was as per dosing ratio given by Ripamonti et al for opioid switching.[17] Those patients where low-dose methadone was added as coanalgesic, opioid semi-switching was done using the method described by Mercadante et al.[18] The dose was gradually titrated up in subsequent outpatient consultations as per requirement.

Following the initiation of methadone therapy, all patients experienced sufficient pain relief. The median daily dose of methadone upon commencement was 5 mg

Table 1 Demographics of patients ($n = 44$)

Items	Numbers	Percentage
Gender distribution		
Male	24	55.81%
Female	20	44.19%
Age distribution (y)		
18–20	2	4.65%
21–40	16	37.21%
41–60	17	37.21%
61–80	9	20.93%
Site of primary cancer		
Bone and soft tissue	8	18.60%
Breast	4	6.98%
Gastrointestinal	3	6.98%
Genito urinary	9	20.93%
Head and neck	8	18.60%
Hematological and lymphoid	1	2.33%
Hepatopancreatobiliary	3	6.98%
Lung	7	16.28%
Primitive neuroectodermal tumor	1	2.33%
Comorbidities		
None	32	74.42%
Hypertension	5	11.63%
Diabetes mellitus	3	4.65%
Hepatitis B	1	2.33%
Multiple comorbidities	3	6.98%
Type of pain[a]		
Somatic nociceptive and neuropathic	24	53.49%
Visceral nociceptive and neuropathic	15	34.88%
Pure neuropathic	2	4.65%
Somatic nociceptive	3	6.98%
MEDD prior to starting methadone (mg)		
60–120	23	53.49%
121–180	5	9.30%
181–240	14	32.56%
>240	2	4.65%
	Median score	Standard deviation
Numerical rating scale for pain (0–10)		
Before starting on methadone	8	1.4
Week 1	3	1.6[b]
Week 2	2	1.6[b]
Week 4	2	1.3
MEDD (mg)		
Before starting on methadone	120	74.9
Week 1	60	40.5[b]

Table 1 (*Continued*)

Items	Numbers	Percentage
Week 2	60	44.5
Week 4	60	24.8
Starting daily dose of methadone (mg)		
At start	5	1.5
Week 1	7.5	2
Week 2	7.5	2.8
Week 4	10	3.2
QTc interval before starting methadone (ms)		
Before starting on methadone	418	25.2
Week 1	447	26
Week 2	428.5	25.1
Week 4	425.5	18.5

Abbreviation: MEDD, morphine equivalent daily doses.
[a]Bone pain in 16, myofascial pain in 7,and opioid-induced hyperalgesia in 2.
[b]$p < 0.01$ on Wilcoxon's signed ranks test.

(SD 1.5 mg), which increased to 7.5 mg (SD 2 mg) after 1 week. All patients were successfully followed up on an outpatient/home care basis with adequate pain control. Among the patients who initiated methadone therapy, none experienced adverse effects such as respiratory depression. Nonetheless, in one patient, we had to discontinue the methadone after 8 weeks due to a prolonged QTc interval and chest discomfort. It is important to note that the median QTc interval remained below 425 milliseconds for the remaining patients. Ten patients developed constipation, in 3 patients, methadone was stopped by treating oncologists, 5 patients continued to be on methadone, 7 stopped by themselves as they had adequate pain control even without methadone, 2 stopped as they went back to villages where they had no access to methadone, 22 patients died due to disease progression within this time, and in 4 patients, interventional procedures were performed for pain management.

Discussion

Methadone is an effective opioid for treating cancer pain, with a safety profile like that of other opioids. Rotation to methadone was helpful in all 44 patients with cancer pain who were being treated in this study. The neuropathic component of the pain in 40 patients may be the cause of its refractory nature. An evidence-based dose conversion protocol[17,18] was used with all the patients, and it was found to be a quick and efficient technique to determine optimal dose of methadone needed in an outpatient context. Neither the MEDD nor the projected methadone dose corresponded to the actual methadone dose that was needed. Considering how refractory pain can be, the MEDD may have underestimated the number of people who needed an increase in opioid dosage but did not receive one. Transitioning from morphine to methadone can present complexities due to the possibility of incomplete cross-tolerance. In future prospective studies, it would be valuable to examine patient-controlled approaches such as the Morley–Makin method as a potential alternative to fixed ratio equianalgesic conversion tables. This is because these patient-controlled regimes enable the use of a lower dosage of methadone (sometimes as low as 1/30th of the previous MEDD) while still achieving satisfactory analgesic effects.[12] In this study, it was observed that a subset of patients ($n = 2$) reported increased pain levels with higher dosages of methadone. It is important to note that the experience of pain in these cases may have been influenced by a range of factors such as psychological, spiritual, or social discomfort. Exploring and addressing these complex issues surrounding pain and its multifaceted nature and opioid safety were beyond the scope of this study (►**Supplementary Material 3**).

Methadone, especially at higher doses, can cause TdP and prolongation of the QTc interval. The risk is higher when the QTc interval is more than 450 milliseconds. Those having a QTc interval at baseline longer than 500 milliseconds should not be initiated on methadone.[19] The median time for QTc was found to be 425 milliseconds in this analysis.

Given the limited participant size and retrospective design of the case series, it is important to approach the interpretation of these findings with caution. Our comparison table also does not include adjuvant analgesics or the different suggested methadone conversion factors. Our results contribute to the mounting body of research suggesting that patients' maintenance doses of methadone may be much different from what is suggested by equianalgesic conversion tables and guidelines.[20]

Conclusion

When conventional drugs and therapies prove insufficient in providing relief for severe and unmanageable cancer

pain, an alternative option is to consider opioid rotation to methadone. The recommended approach for opioid rotation to methadone, as advised by manufacturers, demonstrates both safety and effectiveness, particularly when conducted under appropriate supervision in outpatient settings. Interestingly, our observations indicate that actual dosages of methadone often differ slightly from those obtained through equianalgesic conversion tables and guidelines. Consequently, physicians should not solely rely on conversion tables when opting for opioid rotation, but instead prioritize personalized titration, thorough assessment, and diligent clinical monitoring during and following the rotation process to mitigate the risk of significant adverse effects. Additional research is necessary to explore the potential utility of a modified Morley–Makin approach in facilitating the rotation from other opioids to methadone.

Pointers for Practice

- Methadone is an inexpensive alternative to morphine that is safe for patients with renal failure and provides a longer duration of action.
- It may also have an advantage in treating neuropathic pain, although this has not been conclusively proven.
- However, due to its long and variable elimination half-life, methadone is not ideal when rapid dose adjustments are necessary. Oral methadone should not be increased more frequently than every 4 days.
- Converting doses between methadone and other opioids is complex and can be more dangerous than with other opioids. It is recommended to consult with pain or palliative specialists familiar with methadone use.
- It is important to educate patients and their families about the use of methadone, as they may mistakenly believe that their physician thinks they are an addict.

Disclosure

The responsibility for the writing and content of the article lies solely with the author.

Conflict of Interest

None declared.

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