Original Article

The Use of Methadone in Pediatric Cancer Pain – A Retrospective Study from a Governmental Cancer Center in India

Gayatri Palat[1,2,3], Charlotte Algotsson[4], Spandana Rayala[5,6], Vikranth Haridass[6], Jayalatha Nethagani[7], Vineela Rapelli[6], Maria Gebre Medhin[8,9], Eva Brun[8,9], Mikael Segerlantz[10,11]

[1]Palliative Access (PAX) Program, Departments of [2]Pain and Palliative Medicine, [5]Pediatric Palliative Care, [6]Pain Relief and Palliative Care Society and [7]Radiology, MNJ Institute of Oncology and Regional Cancer Centre, [3]Two Worlds Cancer Collaboration-INCTR, Vancouver, British Columbia, Canada, [4]Faculty of Medicine, Lund University, [8]Department of Clinical Sciences, Oncology and Pathology, Faculty of Medicine, Lund University, [9]Department of Oncology, Skane University Hospital, [10]Department of Clinical Sciences, Oncology and Pathology, Institute for Palliative Care, Faculty of Medicine, Lund University, [11]Department of Palliative Care and Advanced Home Health Care, Primary Health Care Skane, Region Skane, Lund, Sweden

Abstract

Background: The management of cancer-related pain relies on access to opioids. When regular opioids are not tolerated, or are insufficient, methadone is an affordable and effective analgesic. **Aim:** The aim of the project was to describe the pattern of use and clinical experience of methadone in pediatric cancer pain at a governmental cancer hospital in Hyderabad, one of the four Indian cancer centers with permission to prescribe methadone. **Methods:** This was a retrospective study of medical records of all children, under the age of 18, who had been prescribed methadone from September 9, 2017, to November 19, 2019. Data on analgesic effect, prior and concomitant analgesic treatment, opioid side effects, and the handling of methadone were analyzed. **Results:** A total of 11 children were identified and studied. Methadone was introduced mainly when pain was uncontrolled by regular opioids. Initial daily doses ranged from 1 to 15 mg. The duration of treatment ranged from 7 to 307, with a median of 50 days in the nine patients where treatment exceeded one single dosage. Good analgesic effect was reported in 5/9 children, unchanged from previous analgesic treatment in three patients and without any effect in one child. No severe side effects were reported. **Conclusion:** Low-dose methadone in the treatment of pediatric cancer pain at a low-resource cancer center was safe and well tolerated by the patients, with long treatment durations. It was safely managed, administered with single to double daily dosages, hence easy for patients and family to handle, and an affordable treatment option.

Keywords: Cancer, methadone, opioid, pediatric, pain, palliative care

Introduction

Background

Globally, the incidence of childhood cancer is estimated to be around 165 000 new cases annually, of which 80% occur in low- and middle-income countries (LMICs).[1,2] The treatment of cancer-related pain is an important part of supportive care for all cancer patients. Cancer pain is burdensome and has a large impact on many aspects of the patient's life. Pain has been described as one of the most prevalent and problematic symptoms in childhood cancer, causing significant suffering, and is associated with other symptoms such as emotional distress and fatigue.[3,4]

Access this article online

Quick Response Code:

Website: www.jpalliativecare.com

DOI: 10.4103/IJPC.IJPC_109_20

In LMICs, access to cost-efficient options of analgesic therapies is of great importance in the treatment of cancer pain. In 1996, Watanabe *et al*. proposed methadone to be a low-cost option to regular opioids.[5] In a pilot study, of the affordability

Address for correspondence: Dr. Mikael Segerlantz, Palliative Care and Advanced Home Health Care, Sankt Lars Väg 90, 221 85 Lund, Sweden.
E-mail: mikael.Segerlantz@skane.se

Submitted: 24-Apr-20 **Revised:** 07-Jan-20
Accepted: 10-Feb-20 **Published:** 17-Feb-21

How to cite this article: Palat G, Algotsson C, Rayala S, Haridass V, Nethagani J, Rapelli V, *et al*. The use of methadone in pediatric cancer pain – A retrospective study from a Governmental Cancer Center in India. Indian J Palliat Care 2021;27:133-8.

of opioids in 26 countries across the world, oral methadone was reported to be the least expensive opioid (mean price 0.2 USD).[6] In India, strong opioids such as morphine are legally available in the treatment of pain, but the use is hampered by obsolete regulations for opioid prescriptions. The federal state of India has proclaimed opioids as an analgesic therapy in the treatment of cancer pain, but opioids are still not provided in a large number of Indian states.[7]

Methadone

In the recent decade, methadone has received attention as an analgesic for neuropathic cancer pain. Its pharmacokinetic features are characterized by its affinity to the mu-receptor and an antagonistic effect to the *N*-methyl-D-aspartate (NMDA) receptor. NMDA receptors located in the dorsal horn of the spinal cord are the main targets for pharmacological treatment of neuropathic pain.[8] The challenge with methadone is its long half life with individual variations of 8, 5–47 h,[9] and a tissue accumulation and with interactions with many other drugs that also, as methadone, are metabolized in the liver by cytochrome P450.[10] The side effects of methadone are to a great extent equal to those of morphine, including nausea, constipation, and drowsiness.[11] A Cochrane review reported methadone to be efficient in neuropathic pain management and a cost-efficient option in many economies but also that the evidence is yet scarce due to a limited amount of studies.[12,13] However, methadone has been shown to have cardiac side effects such as QT prolongation and in rare cases torsades de pointes[14,15] through its blockage of the human ether-à-go-go-related gene which, in the adult population, causes a dose-dependent effect on the QT interval.[16] In a recent study by Lovell *et al*. from 2019, a clinically significant difference between the incidence of QT prolongation was seen between patients treated with low-dose methadone (mean daily dose of 14.3 mg) and patients treated with high-dose methadone (mean daily dose of 86 mg) with an increased risk of QT prolongation following the higher doses of methadone.[17] Patients with baseline QT prolongation had a higher risk of developing QT prolongation after 2 weeks of treatment compared to patients without a baseline QT prolongation.[18] Clinical studies of low-dose methadone in the treatment of cancer pain in pediatric patients have not been shown any significant increase of the QT interval.[19-21]

Methadone in India

In India, the prescription of methadone is legal since 2014,[7] but only in four governmental cancer centers, whereof at the study hospital since September 2017. There is up till now no national consensus and guidelines for the use of methadone in the management of cancer pain. Methadone is still afflicted by distrust and misconceptions; hence, there is a need for a better understanding and a safe introduction of methadone in India, as well as in other low-resource settings[22] in LMICs over the world.

Aim

The aim of the project was to describe the pattern of use and clinical experiences of methadone in pediatric patients with cancer-related pain at a low-resource hospital in India, one of four Indian cancer centers with a permission to prescribe methadone.

Methods

Study design

The study was implemented as a descriptive retrospective study in pediatric cancer patients who had previously been, or were currently, prescribed methadone at Mehdi Nawaz Jung Institute of Oncology and Regional Cancer Centre (MNJ).

Patient selection

Consecutive data of all pediatric cancer patients, under the age of 18, receiving methadone at MNJ, from the beginning of the permission period, from September 9, 2017, to November 19, 2019, were collected. Patients were identified through a separate register of methadone prescriptions kept by the local staff at the Department of Pain and Palliative Care (DPCC).

Data collection and parameters

Patient-specific information such as gender, age, distance to the hospital, caregiving location (home care, hospital, hospice, or the three in combination), and socioeconomic status were collected. Furthermore, cancer diagnosis and ongoing curative or palliative tumor-specific treatment were documented.

Type of pain was classified as nociceptive, neuropathic, or mixed pain. Indication for methadone treatment was recorded. Documentation of investigations before the initiation of methadone including recent (not older than 2 months) blood tests of sodium, potassium, creatinine, and albumin and electrocardiography (ECG) (not older than 6 months) were registered.

The documented prescriptions of methadone were assessed according to daily dose (mg), number of daily administrations, and type of preparation. Co-existing prescriptions of morphine, fentanyl, tramadol, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), amitriptyline, valproate, and gabapentin were recorded according to daily dose. Morphine equivalent daily dose (MEDD) was calculated according to data provided by the Centers for Disease Control and Prevention for all opioids. The Numerical Rating Scale for Pain (NRS)[23] was sought for. In case of missing data, an assumption of pain as "pain relief" (NRS 0), "mild pain" (NRS 1–3), "pain" (NRS 4–6), or "severe pain" (NRS 7–10) was recorded.

Assumptions of side effects were made due to the criteria of delirium, which were noted in the medical records. The presence of the words "jerky movements," "confusion," "irrelevant talk," or "delirium" was noted as delirium in the study protocol.

Records of the treatment effect of methadone was sought for and followed in patients' medical records. Reasons for discontinuation of methadone were documented, such as side effects, abandonment from treatment, death, or other reasons.

All data were collected from the patients' medical records at the hospital. In a few cases, additional data were collected from the hospice and from the home care files, respectively.

Statistical analysis

Descriptive analysis was used to summarize the demographic data. The obtained data were not symmetrically distributed. Due to the large variety in the results, the median was used as the measure of central tendency. Data calculation was performed with Microsoft Corporation, Excel 2016 (v16.0), Redmond, Washington, US.

Ethics approval

Ethics approval by the Ethical Board of MNJ was obtained before the initiation of the study. The data were compiled in an anonymous manner, and the patients could therefore not be identified.

Results

From the period September 9, 2017, to November 19, 2019, 702 new pediatric cancer patients were referred to the DPCC at MNJ, as first-time registrations, whereof a total number of 11 patients were prescribed methadone.

Patient characteristics

The pediatric patient group consisted of 6 boys and 5 girls, with a median age of 12 (4–16) years. A majority of the children (8/11) came from families living below the poverty line (an annual family income of 20 000 INR or less) and were thus eligible for free-of-charge care through the governmental social security program. The families lived at a distance of 5–640 km from the hospital, whereof 5/11 children lived more than 50 km away.

All the 11 children had an advanced cancer disease and all, but one, received end-of-life treatment. The most common diagnosis was Ewing's sarcoma. At the time of methadone introduction, five children were not receiving any tumor-specific treatment, thus receiving symptomatic care. Of the remaining six children, on oncological treatment, five children were treated with a palliative intent and one child a curatively intent. Patient-specific data are shown in Table 1.

Table 1: Patient characteristics of the pediatric sample (*n*=11)

	n (%)
Gender	
Girl	5/11 (45)
Boy	6/11 (55)
Age (years) - median (range)	12 (4- 16)
Socioeconomic status	
Below poverty line	8/11 (73)
Other	3/11 (27)
Distance to hospital (km)	
<50	6/11 (55)
>50	5/11 (45)
Cancer types	
Ewing's sarcoma	6/11 (55)
Hodgkin lymphoma	2/11 (18)
Rhabdomyosarcoma	1/11 (9)
Wilms' tumor	1/11 (9)
Synovial sarcoma	1/11 (9)
Tumor-specific treatment	
Yes	6/11 (55)
No	5/11 (45)
Intention of tumor-specific treatment	
Palliative	5/6 (83)
Curative	1/6 (17)

Pain and indication for methadone treatment

Pain was characterized as mixed in 8/11 children and neuropathic in 3/11 children at the time of methadone introduction. Indication for switch to methadone from regular opioids was increased or unresolved pain in 10/11 children. In one child, the reason was side effects from the ongoing morphine treatment. Before methadone introduction, a pretreatment ECG was done in 3/11 children and blood tests for sodium and potassium were registered in 5/11 children. Creatinine and albumin levels were assessed in 9/11 children.

Primary opioids before methadone introduction

In 10/11 children, treatment with regular opioids was ongoing, with a median MEDD of 150 (15-240) mg when methadone was introduced. The most common opioid was morphine in 10/11 children: either alone (two children), in combination with fentanyl (one child), or fentanyl and valproate (one child), or in combination with valproate alone (three children), or in combination with NSAID and amitriptyline (one child), or amitriptyline (one child), and NSAID alone (one child). One child was only on paracetamol before methadone introduction.

Methadone treatment

In 7/11 children, methadone was initiated at the pediatric oncology ward at the hospital, in one child at the hospice connected to the study hospital, and in three children through the palliative department's home care service.

In two children, methadone was only prescribed once. For the remaining nine children, the median duration of treatment was 50 (7–307) days. Reason for discontinuation of methadone was death related to cancer disease in three children, a switch to other analgesic regimes in six children, abandonment of care in one child and in one child the reason for discontinuation of methadone was unknown. From the first to the last prescription, methadone doses in the nine patients increased from a median dose of 5 (1–15) mg to a median dose of 22.5 (10–45) mg, respectively. The most common starting daily dosage of methadone was 15 mg (in three children), 1 mg (in two), 5 mg (in two), and in one child each 7.5 mg, 7 mg, 4 mg, and 3 mg. The starting dose was based on calculations of MEDD from the patient's existing opioid doses. These daily methadone doses were divided into one (six children), two (one child), or three (four children) daily dispensations [Figure 1]. All children

received oral methadone, mainly the liquid formulation, but two of the 11 children received pills.

As methadone was initiated, existing analgesic treatment was adjusted, and methadone was combined with morphine (five children), with valproate (one child), with NSAIDs (one child), and with fentanyl and morphine and valproate (one child). The remaining three children thus switched to single methadone treatment. In children where methadone was given for a longer period than 2 months, a single treatment with methadone became the most common analgesic treatment.

Analgesic effect of methadone

Of the 9/11 children who received methadone more than once, methadone was reported to give sufficient analgesic effect in 5/9 children and remained uncontrolled in one child, and in three children, pain remained unchanged [Figure 2].

Side effects

Nausea was documented in three children, and tachycardia was reported in one child. No other side effects were reported.

Discussion

In this study, methadone was used for the treatment of cancer-related pain in a low-resource setting in pediatric patients and in families with low socioeconomic status. Methadone was mainly introduced as an analgesic for mixed and for neuropathic pain when first-line opioid therapy was insufficient. Increased analgesic effect, compared to the previous pain treatment, was found in half of the study group. Pain control was unchanged in all but one of the remaining children, and there were no severe side effects recorded. Unsatisfactory pain relief may have several reasons, including inadequate dosing of methadone, which to an extent can be explained by lack of experience with a new, potent drug and hypothetically a need for additional adjuvant drugs. Furthermore, other causes adding to the experience of pain, such as anxiety, have not been explored in this retrospective review.

In LMICs, methadone is an option of interest as an analgesic drug because of its long-half life and low cost.[6,24] The bioavailability of oral methadone has been reported to be 80%, which is threefold the bioavailability of oral morphine.[25] It contributes to the low number of daily administrations and lower dosage in treatment with oral methadone.

Methadone is a long-acting affordable opioid with analgesic properties beyond those of regular morphine, in that neuropathic pain can be more readily treated. In HIC, methadone has frequently been used as an adjuvant opioid in low doses for the treatment of cancer pain in adults.[12,13,26] Fürst *et al*. discussed the use of very low-dose methadone with the intention to block the NMDA receptor.[27] There are no studies on the use of methadone, as an adjuvant opioid-sparing agent, in children.[21] In LMICs, this approach is potentially interesting since it could contribute to efficient analgesic therapy for a large number of patients.

Methadone is surrounded by distrust due to individual variations in pharmacokinetics and a risk for severe side effects, such as cardiac effects with QT prolongation. Methadone is considered to be difficult to titrate with its unique pharmacokinetic and pharmacodynamic features, and therefore, experience is needed before usage. Before the introduction of methadone, baseline ECG was performed only in a minority of the patients in the present study. Even though ECG was not regularly followed up during methadone treatment, no reports of cardiac events were seen. In the literature, follow-up with ECG is recommended during methadone treatment in adults,[10] but in the use of low-dose methadone (<30 mg daily), cardiac adverse effects are uncommon and the necessity for ECG monitoring might be questioned. The necessity for ECG in pediatric oncology patients may also be questionable in the presence of data, suggesting that QT prolongation is uncommon in children.[21,28] All types of medical investigations come with

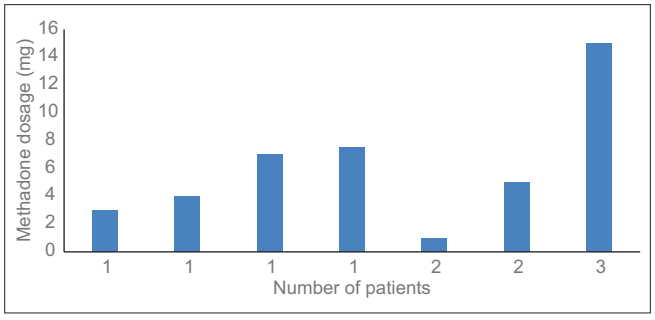

Figure 1: The most common starting daily dosage of methadone was 15 mg (in three children), 1 mg (in two), 5 mg (in two), and in one child each 7.5 mg, 7 mg, 4 mg, and 3 mg. These daily doses were divided into one (six children), two (one child), or three (four children) daily dispensations

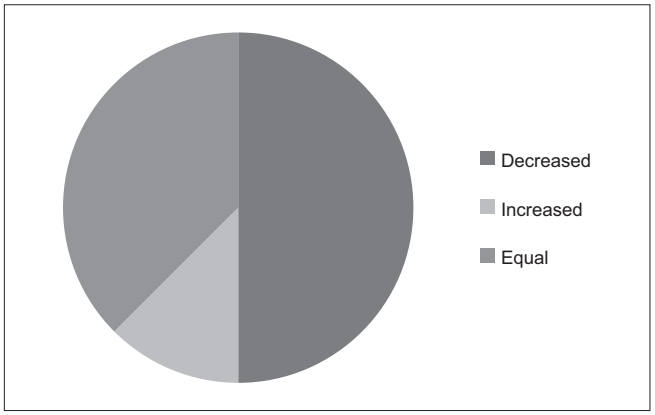

Figure 2: Patients' pain estimation from the first to the last assessment of methadone treatment in the pediatric sample. Pain was assessed from patients' records according to "pain relief" (NRS 0), "mild pain" (NRS 1–3), "pain" (NRS 4–6), and "severe pain" (NRS 7–9). Of the 9/11 children who received methadone more than once, methadone was reported to give sufficient analgesic effect in 5/9 children. In other cases, pain remained uncontrolled (1/9), and in the remaining 3/9 cases, pain assessment was unchanged

a cost, and often lead to further tests, which lay an extra burden on a low-resource facility where all measures must be scrutinized. In the use of high-dose methadone (>100 mg daily doses), concurrent therapy with medications with QT prolongation effects, or interaction with the metabolism of methadone and/or concurrent electrolyte abnormalities, ECG has an undisputed role and dose changes should be monitored cautiously.[21,26]

Methadone is the only long-acting opioid available in a liquid form, and the children in the present study were mostly prescribed the oral suspension. Methadone was prescribed during end-of-life treatment for a period of a median of 50 days without any reported severe adverse effects. This is in line with previous studies in children with advanced cancer[20,29] and well tolerated with few side effects and in the majority of cases a decreased level of pain.[12,13,28] Pain assessment was unfortunately not done, or not available, in almost half of the patients in this study. However, some children were on prescription with methadone during a long period of time, a year or more. The duration of prescriptions without interruption or change of medication indicates some analgesic effects.

In the low-resource setting with a high patient burden, a low-cost and efficient analgesic therapy is needed, and methadone is an example of a cost-efficient opioid option. The important task to introduce methadone in the low-resource setting requires robust and simple guideline and relies on reports from the real-world experiences from studies such as this. A general use of low-dose methadone as an analgesic in cancer-related pain can be supported provided that methadone is handled with caution and attention, with guidelines and customized rules for the low-resource setting.

Conclusions

Methadone, in low dose, in analgesic treatment for pediatric cancer patients, was safely introduced at a governmental cancer hospital in the lower socioeconomic tier. Only few, and no severe, side effects were recorded during the long periods of treatment. With a few daily dosages and affordable costs, low-dose methadone is an important opioid alternative in pediatric oncology care in LMICs, and robust guidelines need to be established.

Acknowledgments

We wish to thank MNJ and the DPCC for providing resources and records for this study and also thank the Two Worlds Cancer Collaboration, Vancouver, Canada, and Pain Relief and Palliative Care Society, Hyderabad, India, for providing resources and support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Cancer Tomorrow. Lyon: International Agency for Research on Cancer; 2018. Available from: https://gco.iarc.fr/tomorrow/home. [Last cited on 2019 Oct 10].
2. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019;144:1941-53.
3. Pöder U, Ljungman G, von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: A prospective, longitudinal study. J Pain Symptom Manage 2010;40:661-70.
4. Hedström M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: Child, parent, and nurse perceptions. J Pediatr Oncol Nurs 2003;20:120-32.
5. Watanabe S, Belzile M, Kuehn N, Hanson J, Bruera E. Capsules and suppositories of methadone for patients on high-dose opioids for cancer pain: Clinical and economic considerations. Cancer Treat Rev 1996;22 Suppl A: 131-6.
6. De Lima L, Pastrana T, Radbruch L, Wenk R. Cross-sectional pilot study to monitor the availability, dispensed prices, and affordability of opioids around the globe. J Pain Symptom Manage 2014;48:649-590.
7. Palat G, Chary S. Practical Guide for Using Methadone in Pain and Palliative Care Practice. Indian J Palliat Care 2018;24: S21-S29.
8. Deng M, Chen SR, Pan HL. Presynaptic NMDA receptors control nociceptive transmission at the spinal cord level in neuropathic pain. Cell Mol Life Sci 2019;76:1889-99.
9. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone-metabolism, pharmacokinetics and interactions. Pharmacol Res 2004;50:551-9.
10. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, *et al*. Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014;15:321-37.
11. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, *et al*. Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. J Pain 2003;4:231-56.
12. Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Database Syst Rev 2017;2:CD003971.
13. Mercadante S, Bruera E. Methadone as a first-line opioid in cancer pain management: A systematic review. J Pain Symptom Manage 2018;55:998-1003.
14. Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. Am J Health Syst Pharm 2009;66:825-33.
15. Pearson EC, Woosley RL. QT prolongation and torsades de pointes among methadone users: Reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf 2005;14:747-53.
16. Kornick CA, Kilborn MJ, Santiago-Palma J, Schulman G, Thaler HT, Keefe DL, *et al*. QTc interval prolongation associated with intravenous methadone. Pain 2003;105:499-506.
17. Lovell AG, Protus BM, Saphire ML, Kale SS, Lehman A, Hartman A. Evaluation of QTc interval prolongation among patients with cancer using enteral methadone. Am J Hosp Palliat Care 2019;36:177-84.
18. Reddy S, Hui D, El Osta B, de la Cruz M, Walker P, Lynn Palmer J, *et al*. The effect of oral methadone on the QTc interval in advanced cancer patients: A prospective pilot study. J Palliat Med 2010;13:33-8.
19. Anghelescu DL, Patel RM, Mahoney DP, Trujillo L, Faughnan LG, Steen BD, *et al*. Methadone prolongs cardiac conduction in young patients with cancer-related pain. J Opioid Manag 2016;12:131-8.
20. Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatr Blood Cancer. 2017;64. doi: 10.1002/pbc.26614.
21. Habashy C, Springer E, Hall EA, Anghelescu DL. Methadone for pain management in children with cancer. Paediatr Drugs 2018;20:409-16.
22. Rajagopal MR. Methadone is now available in India: Is the long battle over? Indian J Palliat Care 2018;24:S1-3.
23. Downie Pal WW, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis 1978;37:378-81.
24. Peirano GP, Mammana GP, Bertolino MS, Pastrana T, Vega GF, Russo J, *et al*. Methadone as first-line opioid treatment for cancer

pain in a developing country palliative care unit. Support Care Cancer 2016;24:3551-6.
25. Davis MP, Walsh D. Methadone for relief of cancer pain: A review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer 2001;9:73-83.
26. Chalker C, O'Neill H, Cranfield F. Efficacy of low-dose and/or adjuvant methadone in palliative medicine BMJ Supportive & Palliative Care Published Online First 2019. doi: 10.1136/bmjspcare-2018-001695.
27. Fürst P, Lundström S, Klepstad P, Strang P. The use of low-dose methadone as add-on to regular opioid therapy in cancer-related pain at end of life: A National Swedish Survey in specialized palliative care. J Palliat Med 2020;23:226-32.
28. Davies D, DeVlaming D, Haines C. Methadone analgesia for children with advanced cancer. Pediatr Blood Cancer 2008;51:393-7.
29. Madden K, Mills S, Dibaj S, Williams JL, Liu D, Bruera E. Methadone as the initial long-acting opioid in children with advanced cancer. J Palliat Med 2018;21:1317-21.