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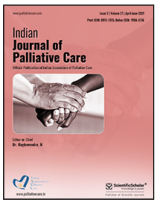

Original Article

The Introduction and Experiences of Methadone for Treatment of Cancer Pain at a Low-resource Governmental Cancer Center in India

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ABSTRACT

Objectives: This study aimed to describe the clinical experience of the health-care professionals (HCPs) responsible for the introduction of methadone, for the treatment of complex cancer pain, at a low-resource hospital in India in a patient-group, burdened by illiteracy, and low socio-economic status.

Materials and Methods: Ten HCPs: Four medical doctors, four nurses, one pharmacist, and one hospital administrator were interviewed. The interviews are examined using a qualitative conventional content analysis.

Results: The interviews showed a confidence amongst the HCPs, responsible for the safe introduction of methadone in a stressful and low-resource surrounding, to patients with cancer pain and the different aspects of methadone, as initiation, titration, and maintenance of treatment.

Conclusion: Introduction of methadone for cancer pain management is safe and feasible although low resources in a challenging hospital setting and care environment.

Keywords: Methadone, Analgesia, Cancer, Pain, Palliative care

INTRODUCTION

Treatment of pain is paramount in the care of cancer patients, whether the pain is caused by the disease itself or by procedures and therapies involved in the care. Pain control is crucial for the patient's quality of life (QOL) and for the patient's confidence toward health-care professionals (HCP) involved in the care and is thus of critical importance for the compliance to medical care.[1-3] However, to accomplish an individualized pain-treatment several prerequisites needs to be met. First and foremost a good awareness and understanding of the importance of pain-assessment, a knowledge of the indications and contraindications, the pros and cons of different pharmacological treatments and in addition to this also the non-pharmacological treatment options that are feasible and available.[4] Moreover, the access to internationally recommended drugs is absolutely fundamental and indispensable, that is, that these drugs are available and affordable and of no difficulties for the patients to access.[5,6]

The World Health Organization (WHO) has listed opioids as essential medicines, that is, medicines for worldwide priority healthcare needs. However, the access to opioids is very unevenly distributed globally with vast and unacceptable disparities between developed and developing countries.[7] Treatment of pain can on a global level roughly be compared by the legitimate medical use of opioid-based analgesics. It was estimated, in 2010, regarding legal global opioid consumption in the treatment of pain that four High Income Countries accounted for 68% of the worldwide consumption, while all Lower-Middle Income Countries (LMIC) together only accounted for 7% of the global use.[6,8] Furthermore, it is estimated that 83% of the worlds' population is left

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without effective pain treatment.[9,10] This is despite improved knowledge in the field and actions taken by different organizations, among them the WHO, to relieve the global burden of cancer pain.[9,11]

In 2012, the European Society for Medical Oncology's Palliative Care Working Group and Developing Countries Task Force presented an overview of conceivable barriers which may limits the access to opioids and treatment of cancer pain. In India, The Indian Association of Palliative Care and many other civil societies, non-governmental organizations and individuals launched a successful advocacy campaign to improve access to opioid medications for medical use. The Supreme Court of India then issued claims to all Indian States to ensure availability and ease of access to opioids for adequate cancer pain management end-of life. In the year 2014, the Government of India amended the old Narcotic drugs and Psychotropic Substance Act with an intention to simplify the regulation around procurement of opioids medications under the category "Essential Narcotic Drugs" but today opioids are still not provided in a large number of Indian states.[6,12]

In India, opioid-treatment is still hampered by misconceptions, doubtlessly due to the lack of proper training and knowledge in pain management amongst HCP.[13] The global needs of opioids, for the treatment of cancer pain, can be met as morphine is inexpensive to produce and largely not protected by patent restrictions.[6]

Methadone - an opioid for the treatment of neuropathic pain

Methadone is often used as an adjuvant analgesic (as an add-on), to an existing opioid (mainly morphine) treatment.[14,15] Methadone as replacement for morphine, as a primary opioid, is frequently used in patients with persisting pain despite high doses of regular opioids, and when opioid tolerance during treatment with morphine occurs.[16,17] It is also applied in patients suffering from non-acceptable side effects from regular opioids, as hyperalgesia, or in patients with kidney-failure.[18]

Methadone is an opioid that was initially developed in the 1940s, as an alternative to morphine. It has been widely used to treat heroin-addiction but has in the recent decade received more attention as an analgesic for neuropathic cancer pain.[16,17] Methadone in pain-treatment is afflicted by distrust.[19,20]

Methadone's pharmacokinetic (PK) and pharmacodynamic (PD) features are characterized by its affinity to the mu receptor and an antagonistic effect to the N-methyl-D-aspartate (NMDA)-receptor. The NMDA-receptors located in the dorsal horn of the spinal cord are the main targets for pharmacological treatment of neuropathic pain.[17] The challenge with methadone is it's long half-life with individual variations of 8.5–47 h,[19] a tissue accumulation and interactions with many other drugs that also, as methadone, are metabolized in the liver by cytochrome P450.[20] Methadone has been showed, in the adult population, to have cardiac side effects and to cause a dose-dependent effect on the QT-interval, which in rare cases could result in a drug-induced Torsades de Pointes (*diTdP*).[21-23]

Other side effects of methadone are to a great extent similar to those of morphine, including nausea, constipation and drowsiness.[24]

Prescription of methadone is legal in India since 2014, for pain management, but only in use in a few centers,[25] whereof the present study hospital is one, since Sep 2017.[26,27]

A proper understanding of methadone's potential as an analgesic and the side-effects is essential for the safe introduction, in India as well as in all LMIC worldwide.[13]

Aim

The aim with this report was to share the experience, from different perspectives, from different HCP, in introducing a highly potent and efficient and affordable drug for treatment of cancer pain in a low-resource setting.

We hope this report can serve as an encouragement for similar care facilities to consider the use of methadone in the treatment of cancer pain, especially when elements of neuropathic pain are present.

MATERIALS AND METHODS

A semi-structured interview technique was applied with the purpose to review the experiences from the HCP of methadone treatment for cancer pain, both in pediatric and in adult patients. Interviews took place at the hospital with the main researcher conducting all the interviews. Data were collected from the content of the interviews and analyzed using qualitative conventional content analysis, that is, a thematic analysis approach.

Study hospital

Mehdi Nawaz Jung Institute of Oncology and Regional Cancer Centre (MNJ), is a governmental cancer-hospital in Hyderabad, Telangana, with a catchment area of approximately 35 million inhabitants. The hospital provides cancer treatment to approximately 10,000 new cancer patients on a yearly basis with care, free-of-charge for patients below the poverty line. The MNJ hospital is one of few cancer-centers in India with permission to prescribe methadone with a license since 2017.[28]

Study participants

Eligible HCP were selected by purposive sampling based on their involvement and experiences of methadone in cancer pain at the study hospital. Different professionals were selected to ensure a broad perspective of the responsibilities and viewpoints of methadone-usage. In total ten HCP were eligible and approached, of which two of these (GP, SR) also are co-authors to the article but not involved in the design of the interviews or the coding of the results. Interviews were conducted between November 27, and December 3, 2019.

Data collection

Interviews were created based on topics perceived as important issues, covering HCP perceptions on safety and logistic aspects concerning methadone in the treatment of cancer pain and formulated by CA, EB, MS, and MGM. Specific topics included were; regulations in procurement and prescribing methadone, when to consider methadone treatment, comorbidities and contraindication to assess before initiating methadone, base-line investigations (lab testing and ElectroCardioGram) before initiation of methadone, protocol for initiation and dose escalating of methadone, opioid-rotation to methadone, monitoring of side effects, amount of methadone prescribed each time and iterations, concerns about addiction, instructions about methadone to patients and caregivers, and positive and negative experiences of methadone compared to morphine (*full topic list, see appendi*x). The main researcher, CA, conducted all of the interviews in English. All interviews were audiotaped and transcribed verbatim by CA (*for interviews, see appendix*).

Data analysis

We reviewed the transcribed interviews by adopting a conventional content analysis method.[29] The analytic steps we used, as described by Hsieh and Shannon: First a thorough reading of the text and then subdividing it into content-areas for every interview questions separately. We then extracted and condensed significant meaning units and made abstractions and code-labeling. We sorted the codes into categories and created sub-themes. Finally, we decided on themes, by grouping codes around larger meaning-units whose content reflected the meaningful data in the interviews. The data were coded by MS. A member checking of the data and conclusions, to increase the credibility of the study, was done by all authors.

Ethics approval and consent to participate

Ethics approval by the ethical board of MNJ was obtained before initiation of the study, as part of a larger retrospective review of patients receiving methadone in the treatment for cancer pain, since MNJ was granted license in 2017. Permission for this study was also applied for and obtained from the head of the department of Department of Pain and Palliative Care at MNJ hospital. Informed consent to participate and permission for the audio recording of discussions was obtained from each participant before the interview.

RESULTS

The included HCP, four medical doctors, four nurses, one pharmacist, and one hospital administrator were interviewed. An interpreter participated during the interviews of three of the four nurses and the pharmacist.

Data-analyses of the collected interview-results, from all the participating HCP led to the finding of 34 primary codes, 15 sub-themes, and seven main themes. [Table 1] displays the main themes, sub-themes, and primary codes.

According to the seven main themes we have, to facilitate for the reader, interpret, and summarized the contents and findings from the interviews (text data).

The requirement to procure and dispense methadone

In India, the prescription of methadone was legalized 2014. Today, any hospital can apply for a license to procure methadone but up until now only a few centers have a license, whereof at the study hospital since September 2017. A hospital has to go through a license process to achieve a Recognized Medical Institution (RMI) – status, which entails several steps to ensure a safe use of methadone. A hospital is required to have sufficient facilities to see patients, a facility to safely store methadone and trained Recognized Medical Practitioners, for the usage of and prescription of opioids. The Drug Control Authority (DCA) then issues a certificate of RMI. The hospital then makes a request to DCA for an estimated annual requirement of methadone prescription.

Procurement of methadone

The DCA issues the hospital, according to the annual requirement of methadone, to procure and purchase the needed amount and desired medical formulation. The Hospital Purchase Section, or as per the hospital protocol, then approaches pharmaceutical companies, with a license to manufacture methadone, and calls for quotations. A hospital committee, consisting of the head of the department, head of the hospital, administrator officer and the resident medical officer, reviews the quotations, and the different tenders and then decides which pharmaceutical company that has quoted the best price and thus which company to approach.

Special concerns when prescribing methadone

A patient history of arrhythmias, due to QT-prolongation, or an end-stage liver cirrhosis are considered as contraindications and such patients will not be considered for methadone treatment. The side effects of methadone are similar to those seen with other opioids. Drowsiness and confusion are the most frequent side effects experienced with methadone.

When to consider methadone treatment

Methadone could be considered in multiple different situations; in a more complex pain situation with unresolved pain despite treatment with regular opioids, in situations with uncontrolled side effects of morphine or of any other regular opioids, as well as in patient with renal failure. Furthermore, an opioid-rotation, to methadone, is an option when morphine induced tolerance is a clinical issue with or without opioid-induced hyperalgesia.

Table 1: Formulation of themes.

Themes	Subthemes	Codes
The requirement to procure and dispense methadone		
	Recognized Medical Practitioner (RMP)	Any medical doctor can prescribe opioids
		Doctors in India are not trained in using morphine or similar opioids
		Trainee is needed
		Training in pain and palliative care
		Special training in using methadone is encouraged
	Recognized Medical Institution (RMI) - status	The license to procure methadone was released by government of India 2014
		Any government hospital can apply for a license to procure methadone
		Drug control authority and certificate
		Annual counter of methadone, what formula is needed.
Procurement of methadone		
	Hospital purchasing departement	Committee consisting of four people
		Quotations
		Pharmaceutical companies
Special concerns when prescribing methadone		
	comorbidities	Older patients
		Drug-interactions
	contraindication	QT prolongations. Liver cirrhosis
	side-effects	Drowsiness. Confusion.
When to consider methadone treatment		
	Neuropathic pain	Unresolved pain on morphine
		Complex neuropathic pain syndrome
	Side-effects to morphine	Morphine induced tolerance
		Hyperalgesia
		Drowsiness. Confusion.
		Renal failure
Base-line investigations before prescribing methadone		
	Lab-testing	Electrolytes
	ECG	QT-prolongation
Methadone doses		
	Initiation	First-line opioid
		Add-on opioid
	Escalation	Go slow
	Opioid-rotation	Three-day slow-conversion method
Prescription of methadone		
	Safety	Instructions to patients and caregivers
		Storages of methadone
		Addiction
	Dispenses of methadone	Formulation of methadone
		Amount of methadone
		Refills of methadone

Baseline investigations before prescribing methadone

The extent of baseline investigations depends on where the patient is in the trajectory of the disease. That is, if the patient is receiving treatment with a curative or palliative intent, or if the patient is in a situation close to end-of-life care. In a situation with an ongoing curatively intended treatment, especially in patients receiving chemotherapy, where nausea and vomiting is frequent, electrolyte balance is an issue that must be monitored. Similarly, in patients with comorbidities and multiple medications, drug-interactions and QT-prolongation could be a valid concern.[30] In a palliative stage of a disease, in end-of-life care, the focus of care is QOL and comfort. Medical investigations that expose patients for painful and/or futile procedures must then be scrutinized.

Methadone doses

- Methadone could be used as an *adjuvant opioid*, in low doses of 2–2.5 mg once or twice daily, to a regular opioid, as morphine. This is especially successful when a neuropathic pain component is suspected and in a situation with an increased risk of side-effect following a dose escalation of morphine.
- Methadone could also serve as a *first-line opioid*, and thus as a primary opioid. When initiating methadone to opioid naïve patients, in a safe way, the "start low and go slow" method, with doses escalations of 2–2.5 mg once or twice daily, with a 5 days interval is recommended.
- -When preforming an *opioid-rotation*, from a regular opioid as morphine to methadone, a 3-day slow-conversion method could be employed. The first step is then to calculate the mean equivalent dose of morphine (MEDD), that is, the existing dose of morphine during 24 h, then to use a morphine-methadone conversion ratio chart to identify the equal dose of methadone. To overcome cross-tolerance the methadone dose then must be reduced by 50%. The remaining 50% will preferably be added in a period of 3 days, the 1st day one third of the dose is added, the 2nd day a dose escalation to two thirds, and the past day the full dose is added. Simultaneously, morphine is reduced by one third, two thirds, and then completely withdrawn the 3rd day.

Prescription of methadone

Instructions to patients and caregivers about methadone usage, potential side-effects and how methadone is safely stored in their home, is important. There is however no need for greater concerns of addiction to methadone compared to that of regular opioids. A responsible prescription of any opioid is warranted. Dose-titration must be monitored in close contact with the patient or with the caregiver. Daily follow-ups are recommended for in-patients at the hospital or hospice and by daily telephone calls to patients in a home-care setting, to assess the treatment-response and side-effects during the 1st week. If the patient responds well to methadone, the sum of 1–2 weeks of methadone consumption, either with pills or with syrup, is prescribed from the hospital. If the patient resides far away from the hospital a prescription for up to 1 month is dispensed. The methadone formula (pill or syrup) is decided on the patients' convenience. The pill is the easiest and safest way to prescribe methadone, with a reduced risk of misunderstanding or miscalculation, compared with the equipotent dose of the syrup formula. On the other hand, in patients with dysphagia and in pediatric patients or when the patient is prescribed very small amounts of methadone the syrup is preferable prescribed.

DISCUSSION

We can report on methadone being introduced, in a stressful and low-resource surrounding to patients with cancer pain, in a safe manner and with confidence amongst the involved HCP covering the different aspects of methadone initiation, titration and maintenance of treatment.

Methadone is an effective analgesic for the management of chronic complex pain such as neuropathic pain seen in cancer and when the pain does not respond or subsides on regular opioid such as morphine or fentanyl. Methadone could also be a useful alternative in clinical situations with opioid tolerance defined as a decreased analgesic effect of regular opioids after repeated and prolonged use.[31,32] Furthermore, methadone is an affordable option to other long-acting regular opioids, less expensive, and more accessible, which is of special interest in LMIC.[31,32] In fact, the MEDD of Morphine (60 mg) and Methadone (10 mg) is equivalent in cost, 7 Indian Rupee (INR) for Morphine versus 6.75 INR for Methadone, in India (Dr Gayatri Palat, personal communication, June 15, 2020).

Methadone is afflicted with misbelief and with an underserved bad reputation of being unpredictable and difficult to monitor.[19,20] and thus with great risk of severe side effects such as *diTdP*.[21-23] True, the distinct PK and PD properties of methadone require caution when a patient is initiated, titrated, and maintained on methadone. The required dose of methadone, to obtain an analgesic effect, varies from one patient to another due to inter-individual variations but also if any drug-interaction occurs interfering with the PK and the PD. However, in a recent study by Lovell *et al*. from 2019 a clinically significant difference between the incidences 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 following the high doses.[33] 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.[33] Clinical studies of low-dose methadone in the treatment of cancer pain in pediatric patients have not showed any significant increase of the QT-interval.[34,35]

A low to moderate dose of methadone, as first-line and primary opioid or as an adjuvant opioid, could therefore be considered as a safe treatment of complex cancer pain.

That being said, it is essential that HPC (physicians) prescribing methadone undergo trainee program, in pain management and palliative care with a special focus on methadone, to obtain a good understanding of its usage and the importance of adherence to recommendations, to avoid any serious adverse events. Dose-titration must be monitored in close contact with the patient or with the caregiver. In addition, HCP must ensure that patients and caregivers are provided with clear and easily understood instructions about methadone use, potential side effects, and how methadone is safely stored in their home.

Limitations

Content analysis always involves some level of subjective interpretation. Due to the limited number of participants (ten HCP) and the heterogeneity in their professional role and thus in experiences, findings must be read with some caution. Qualitative approaches have limited generalizability outside the scope of participants' lived experiences and other clinical settings. The transcribed verbatim interviews' are attached in an appendix for full transparency.

CONCLUSION

Methadone, in low doses, as the primary opioid, in treatment for complex cancer pain, in a low resource setting, can be safely introduced. Involved HCP, from different categories were confident. Proper training of staff in pain management, clear guidelines on opioid-treatment, and patient - and caregiver education is essential.

Acknowledgment

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Authors' contribution

Substantial contribution to study conception and design and drafting of the manuscript: CA, MS, EB, M G-M, GP, and SR. Interviews and transcription verbatim: CA. Data analysis and interpretation of data: CA, MS, and EB. All authors read and approved the final manuscript.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Name: Dr G, prescriber of methadone

Title: MD, head of the department

Date: (2019-12-03)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting.

Question only to MD as the head of the department:

What is required, in professional training, to be allowed to prescribe methadone?
As per Indian law, any doctor can prescribe opioids. But, you will not get it. You need special license to procure and dispense. That is where the trainee is needed. You can undergo special training in palliative care, even though it is not a formal training (as per the government). When they give license, they look at elements of some kind of training in pain and palliative care before they give license to procure morphine and methadone. But, we generally encourage that methadone needs much more detailed training after you have been trained in using morphine.

First of all, doctors in India are not trained in using morphine or similar opioids. The doctors who are trained in using morphine and other opioids should undergo further training in using methadone. It needs more detailed training than other opioids.

Questions to MD as a prescribing doctor prescribers:

When do you consider initiating methadone-treatment in a patient?
- Upfront (as first-line opioid)?
- When failure on morphine? If yes- what morphine-dose?
- Any particular diagnosis?
- Nociceptive or neuropathic pain?
- Other situations?

It depends on what indication you are looking at. It can be used as first-line, it can be used as adjuvant medication ("add-on") or it can be used as substitute medication in terms of opioid rotation (switch from one strong opioid to another strong opioid).

We don't say that if you have failure on morphine, then you use methadone. When there is a definite pain syndrome, typically we feel that there is a component of neuropathic pain, we feel that when morphine doesn't work methadone may be helpful. We have seen that it is actually working better than morphine in complex, neuropathic pain syndromes. There are no upper limits on morphine doses, it is not that you switch to methadone when the patient is using a certain morphine-dose. You can keep building up the dose of morphine until you get pain-relief but sometimes when you increase the morphine, the patient starts feeling drowsy or gets confused. In those situations you cannot increase the morphine dose, in that situations we switch to methadone and see if it can be better.

Methadone treatment have different indications. We use methadone in complex neuropathic pain syndromes, then it is very helpful to use methadone over morphine. We use methadone for opioid rotation, when the patient develops morphine induced tolerance, hyperalgesia or neuro-excitability we switch over to methadone and find it to be very helpful. We also use methadone if the patient has developed unacceptable side-effects to morphine, like severe constipation.

What special concerns do you have when prescribing methadone - any comorbidities or side-effects that are of special interest?
It all depends on what stage of disease the patient is in. If the patient is still healthy and receiving treatment with curative intent then surely I will be concerned about electrolyte imbalance, especially if the patient is on chemotherapy and vomiting. Similarly, if the patient is on multiple medications I will be worried about inducers and inhibitors of the medications. I would be cautious if the patient were using methadone together with many other medications and I'll therefore go through the list

and see which medications the patient is using. The concern is mostly QT-prolongation which we see with methadone and especially in combination with other medications or sometimes with overdose of methadone.

QT-prolongation, drug-interactions and delayed peak of action. Sometimes we see patients after five or six days and they are then becoming drowsy, which we may miss if we don't follow them up on a regular basis. That will be a main concern of mine. We prefer to follow patients for a long time after methadone introduction.

When we see the patient in hospice care, end-of-life care, we are looking at the quality of care. We will not spend too much time to investigate or looking at electrolyte imbalances because our focus is goal of care which will be comfort care and hospice care.

Do you have concerns about addiction following the methadone prescription?
Not at all. Of course, we should use all opioids with caution. We should be responsible for correct prescription of any opioid for that matter, not especially methadone. We should take the same care that we would for any other opioid, when using methadone.

What are the requirements in the regulations when you prescribe methadone?
As per the regulation you have to apply for a special licensing process, we call it a recognized medical institution (RMI)-status. To get that status there are some requirements. We should have a facility to see patients, a facility to safely store methadone and doctors trained in the usage of opioid prescriptions. It is the same for all opioids.

Having said that, government institutions do not recognize RMI-status. They require a letter to the drug controller. The drug controller prescribes the RMI-status. The government institution writes to the drug controller and kindly asks them to procure this much quantity of opioids. Based on that letter we place an order to the pharmaceutical company.

The trained doctors are recognized as a recognized medical practitioner, RMP.

Are there any contra-indications for methadone?
It is just like any other opioid, when you see a patient in pain and you think the patient is in need of opioids according to step three of the WHO ladder of cancer pain you can use methadone like morphine. This is unless the patient has a past history of QT-prolongation or other cardiac problem that can increase the risk of developing QT-prolongation. I would not think of it as a contraindication, but I would be cautious when using methadone in these situations.

In what cases do you do base-line investigations?
- Lab testing? (Which?)
- ECG?

Ideally in all patients we should have baseline investigations (electrolytes) or ECG when prescribing methadone. Having said that, in most of the patients with advanced malignancy we will not subject them for more investigations or tests because the focus of care in those situations is to give the patient comfort.

What is the protocol you follow to initiate methadone?
It all depends on the patient. If you are starting methadone as an adjuvant medication we start methadone in small daily doses of 2-2,5 mg 1x2. Starting dose of methadone as a first-line opioid would be I would start very low and go slow, a daily dose of 2-2,5mg 1x2. Because we are all learning, it is a very new drug that we recently received in India, for the institution to follow certain protocol. We started with a three-day slow-conversion method. First day, we calculate mean equivalent dose of morphine (MEDD). The first day the patient gets one third of MEDD, the second day two thirds of MEDD and the third day the patient gets a full dose. 1-2-3 day-conversion method. Look at methadone-morphine conversion ratio, there is a table chart which shows the dose daily mean equivalent dose of morphine converted to the equivalent dose of methadone. Then, 30-50% has cross-tolerance and we reduce the dose of methadone – and that we start as one third of the dose on the first day, two thirds on the second day and full dose on the third day.

To summarize, we will first calculate mean equivalent dose of morphine (24h dose) and look at the chart to see the equal dose of methadone. Once we get the dose of methadone, we reduce it by 50% to overcome cross-tolerance. The remaining 50% we will add on a period of three days, one third, two thirds and full dose. Similarly, we reduce morphine by one third, two thirds and then we completely stop morphine.

The idea is to go slow, because we are learning to understand how methadone behaves in our patient population. That's why we adapted this institution protocol, but slowly we are getting more confident to use methadone as a first-line opioid and as an adjuvant medication.

What makes you decide on pills or syrup?
Patients' convenience. I prefer tablets when the patient can swallow these. Syrup when patient cannot swallow, finding it difficult to swallow or in paediatric patients. Also, when you need smaller concentrations we use syrup. I prefer tablets, because when you send the patient home with a certain amount of medication it is very difficult for them to calculate the syrup, tablets are easier. When you need finer calculations of 1 mg then you must use syrup, since tablets are 5mg. Prefer tablet in adult patients.

How is the analgesic effect and dose-titration monitored? By whom (doctor, nurse)?
With the present protocol we are using it in a difficult pain syndrome. I would therefore like to follow the patient almost daily for a week-long period until I know the dose that the patient requires and whether the patient is opioid-responsive or not. I would like to monitor the patient for a week-long period.

If the patient is an in-patient or in hospice I would follow up, as a physician. If the patient is coming from home-care it may not be possible to follow them on a daily basis. If possible, we ask our nurse (we designate one nurse per patient) to call the patient daily until the next week. The nurse then reports to me how the patient is doing, their response to the treatment or if they experience side-effects.

How do you decide on the amount of pills/millilitres you prescribe each time?
Depends on how stable the pain of the patient is. If it is a very unstable kind of pain or I am unsure if the opioid responsiveness of the patient, I will not be prescribing for more than one week. If the patient is having a stable pain that responded very well to methadone, then maybe I will prescribe for ten days or two weeks. Most opioids that we prescribe from the institution, we don't prescribe for more than ten days or two weeks´ time unless the patient is coming from a very "far away" place. In those cases, we prescribe for almost a month.

There is no restriction or standard guideline.

How much do you prescribe each time and how often can the patient refill?
They can come for refill depending on how stable the patients' pain is and the condition of the patient. If the patient is having a progressing cancer, the need may change very rapidly so we have to have more frequent follow up – maybe weekly or more often. If the patient is having stabile pain, they will come for refill every two weeks.

What are your positive experiences of methadone over morphine?
I have seen some dramatic response to methadone, especially on patients who received morphine without pain-relief but with unpleasant side effects such as constipation, confusion, nightmares and myoclonus. When we switched them to methadone the response was dramatically improved, they got good pain-relief without side-effects. You don't need to give it fourth hourly – it is just twice a day or sometimes three times a day. If the patient responds to methadone it is a nice medication to use in terms of an analgesic.

Have you had any negative experiences from methadone-treatment? If so- what?
I could never attribute to methadone if the patient died suddenly, if it wasn't because of progressive disease. I did notice a severe drowsiness or delirium in four to five patients. When we reduced methadone they came around, which was a learning process for us that we must be very careful about dose-titrations.

Do you give advice and instructions about over-dosage and how to treat this to the patient?
What we tell them, as for any opioid, when we prescribe is that they will develop constipation, there is a chance that they may develop nausea or vomiting and if that is the case they should continue the treatment. We also tell them that if they notice any signs of undue drowsiness, which means feeling drowsy while talking, please report to us. If the patients family is noticing that the patient is behaving differently, talking irrelevantly or having abnormal movement of the limbs please report to us. We tell them this as a standing instruction. Lastly, we also tell them that if the pain is not responding or increasing, do not wait until the next appointment. They can come back at any time.

Regarding opioid-rotation; what method do you use to convert morphine to methadone?
Mean equivalent dose of morphine, 50 % reduction to methadone for cross-tolerance. Then, 50% 1/3 first day – 2/3 second day – full dose on the third day. As for morphine, first day I'll reduce the dose of morphine to 1/3, on the second day to 2/3 and on the third day I'll stop morphine prescriptions. That is the kind of protocol we developed but some patients can start straight away without undergoing morphine as a first-line opioid and in some patient methadone is used as an add-on treatment. It is a standard protocol, after calculating MEDD – ratios.

Name: Dr S, prescriber of methadone

Title: MD

Date: (2019-12-02)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to MD as a prescribing doctor:

When do you consider initiating methadone-treatment in a patient?
- Upfront (as first-line opioid)?
- When failure on morphine? If yes- what morphine-dose?
- Any particular diagnosis?
- Nociceptive or neuropathic pain?
- Other situations?

Mostly in head-neck cancer and cervical cancers where there is more neuropathic pain than somatic pain. That is when I think of methadone as first-line opioid. Increase morphine first and see. Side-effects.

Usually I think it is the higher doses when we increase morphine first and see if there is any kind of drowsiness or the patients' sedation. If it is not there and the patient is still having pain I still increase it but if the patient develops side-effects of morphine I would definitely consider to shift to methadone.

Most commonly head-neck cancer and cervical cancers. Children with osteosarcomas when the pain wasn't morphine sensitive.

Mostly neuropathic pain but nociceptive too. Requiring high doses of morphine with inadequate pain-relief and neuropathic pain. I would consider using methadone as an add-on treatment so that the patients keep receiving morphine but also methadone for neuropathic pain.

What special concerns do you have when prescribing methadone- any comorbidities or side-effects that are of special interest?
We all ought to be careful of the QT-prolongation that methadone can cause, I don't want to have a (?) so severe that it would decrease the QOL. When the patients are receiving treatment and I plan to start methadone I get them investigated and check their electrolytes and ECG. If it is a palliative care patient close to end-of-life I would probably not get them investigated. We worry about the cardiac side-effects but also sedation and constipation. I think, with instruction we can handle that much better.

Do you have concerns about addiction following the methadone prescription?
No, we have used it for all cancer patients with progressive cancer or very severe pain.

What are the requirements in the regulations when you prescribe methadone?
ECG, electrolytes, physical condition of the patient. Distance where they live – they have to come for refill. I can not give them a huge quantity and then ask them to come after one or two months. The third thing I am very worried about is the compliance. If the child´s family or adult patients are very incompliant I do not start them on methadone. Even after starting methadone, if I see the patient is incompliant I try to tell them and if their compliance doesn't increase I'll draw back the prescription and put them back on morphine, which is much safer.

Are there any contra-indications for methadone?
Maybe a pre-existing heart-condition, there are no absolute contraindications for methadone.

In what cases do you do base-line investigations?
- Lab testing? (Which)?
- ECG?

Someone who has been receiving chemotherapy or radiotherapy since they have a high chance of getting nausea and vomiting and a high risk of developing electrolyte imbalances. A patient whom I expect to live for a longer time of life, even without treatment, I would definitely investigate them and start methadone.

Lab testing? (Which)? Sodium, electrolytes, potassium, calcium.
ECG? Yes

What is the protocol you follow to initiate methadone?
Three-day titration method and rapid switch method, sometimes I start directly. I use the 3-day method when the patient is admitted to hospice or hospital (in-patient setting) because the nurses can tell them and it is not confusing for the patient.

I do the rapid switch if I am seeing the patient in out-patient clinic and I want to rapidly change the medication. It is difficult for the patient to remember different administration-timings (once daily, twice daily etc). I think they would just get confused. I do direct switch if I see someone in severe pain. Rapid switch is when they are on morphine one day and I convert it directly to methadone three times a day.

What makes you decide on pills or syrup?
When we had access to both, we gave pills to adults and syrup to children. When I recommend only two milligrams, I would use syrup since it's easier to do. With tablets you can only do multiples of 2,5mg. When I had both of them, that's how I considered tablet or syrup. Depending again on the compliance of the patient, syrup is difficult to take and there is a risk the patient would take the wrong dose. We are now using only syrup.

How is the analgesic effect and dose-titration monitored? By whom (doctor, nurse)?
Both of us do it, it depends on who of us is seeing the patient first. We monitor the pain relief with the numerical scale. In children it is the ESAS-revised scale. Dose titration is done very slowly. We increase in multiples of 2,5 every day, for example if a patient is on 2,5mg three times a day we would increase the night dose to 5mg.

How do you decide on the amount of pills/milliliters you prescribe each time?
Depends on the distance the patient is travelling to. If they are living in the city I would probably give them a supply of two-three weeks but if they are living 200-300 km away I would give them a supply of one month. It depends on the dose they are taking, I would calculate how much they require every day and multiply it with 30 and that is what I would give them and send them.

How much do you prescribe each time and how often can the patient refill?
In the city: two-three weeks. From rural areas: 30 days. They can come back often, but if they require a lot of methadone I would ask them to come to the hospice for observation because I don't want them to abuse it.

What are your positive experiences of methadone over morphine?
I like to prescribe methadone in patients with difficult pain and neuropathic pain that has not subsided with morphine. It doesn't happen very often but it has excellent effect that way. It has excellent effect in head-neck cancers, it gives good pain-relief.

Have you had any negative experiences from methadone-treatment? If so- what?
There are few adolescents whom I've started on methadone and they said they were more comfortable with morphine than with methadone. I thought methadone would be an excellent drug of choice for them but they came back and said they felt better with morphine.

Do you give advice and instructions about over-dosage and how to treat this to the patient?
I think we use quite low doses of methadone here than in other places, my personal opinion. I do tell them if they feel drowsy, complain of palpitations, might feel a bit dull and not very active to call us. We give them our phone-number and ask them to contact us. I usually don't tell them to skip a dose immediately, but to call us first.

Regarding opioid-rotation; what method do you use to convert morphine to methadone?
Protocols, three-day conversion or rapid switch.

Name: Dr M, prescriber of methadone

Title: MD

Date: (2019-11-29)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to MD as a prescribing doctor:

When do you consider initiating methadone-treatment in a patient?
- Upfront (as first-line opioid)?
- When failure on morphine? If yes- what morphine-dose?
- Any particular diagnosis?
- Nociceptive or neuropathic pain?
- Other situations?

When do you consider initiating methadone-treatment in a patient?
We consider initiating methadone in patients whose renal functions is impaired and in patients who are having inadequate pain-relief with morphine. If they are getting a high dose of morphine we try to switch the patient to methadone and if the patient is having an impaired renal function.

What special concerns do you have when prescribing methadone- any comorbidities or side-effects that are of special interest?
As methadone causes QT-prolongation, we observe the patient if they are having any side-effects like QT-prolongation, palpitations or PDMS or any episode of other side-effect. If any cardiac issues we try to ask this (?) before starting methadone.

Do you have concerns about addiction following the methadone prescription?
No. We have not come across any patient who has been addicted to methadone.

What are the requirements in the regulations when you prescribe methadone?
If the patient is on morphine we try to convert the daily dose of morphine to methadone according to the ratios. Different doses of morphine have different ratios. We try to convert it and then we start the patient on methadone.

Are there any contra-indications for methadone?
A previous history of cardiac problems or severe liver impairment are contra-indications.

In what cases do you do base-line investigations?
- Lab testing? (Which)?
- ECG?

Lab testing? (Which?) In most of the patients we try to do baseline investigations, most of the patients who come here are from "far off" places or do not have any family attendants with them. We try to do baseline investigations on most of the patients but depending on the patients' condition and what time they are coming to us, its difficult to follow up patients. If the patients are elderly and having comorbidities like hypertension or diabetes or if they are on cardio-toxic chemotherapy then we especially make sure we get the baseline investigations done, because of dehydration they often have electrolyte imbalances also.
ECG? Yes, electrolytes (sodium, potassium, magnesium and calcium).

What is the protocol you follow to initiate methadone?
Baseline investigations and the morphine to methadone conversion.

What makes you decide on pills or syrup?
We usually think the conversion, if its in certain milligrams, it is easier to give methadone syrup diluted and titrated to the exact milligram. It is difficult with the tablet form, the tablet we have here is a 5 mg tablet. If the patient is getting 7,5 mg or 10 mg of methadone as a single dos it is easy but if the patient is getting 6mg it is more difficult with the tablet. In those cases we prefer syrup form so that we can dilute it to get the exact dose.

How is the analgesic effect and dose-titration monitored? By whom (doctor, nurse)?
Mostly doctors who monitor, by numerical pain score, and we ask them to take morphine for break-through pain.

How do you decide on the amount of pills/milliliters you prescribe each time?
Mostly the patients are on chemotherapy and have to come every two weeks, 15 days or 21 days. Accordingly, we prescribe for 10-14 days. We try to prescribe for 14-20 days maximum so they have regular follow up. They come from very far off-places and they have frequent telephone follow-up every two or three weeks maximum.

How much do you prescribe each time and how often can the patient refill?
We prescribe for two weeks, so they have to come every two weeks or three weeks for their refill and assessment of the symptoms. Usually if the patient is admitted to hospital observation they can come daily and in the hospice they also come daily. If the patient comes frequently we give them a prescription for five days and calculate how much they have to take daily, then we cross-check with the stock that they are having with them. Initially we give for five days, and then 14 days or 20 days.

What are your positive experiences of methadone over morphine?
Good results in head- and neck cancer patients, especially when they have neuropathic component and myositis post chemotherapy or radiotherapy, huge masses of lymph node involvement and neuropathic pain.

Have you had any negative experiences from methadone-treatment? If so- what?
Few patients have complained of giddiness and palpitations. No severe negative symptoms.

Do you give advice and instructions about over-dosage and how to treat this to the patient?
We instruct them the dose they need to take. Regarding this, we ask them to only take the prescribed dose. If they are having any pain, we ask them to take morphine. If the patient is newly started on methadone, it will take some time to (five-six days) to get the correct result of the drug. We usually don't increase the dose and ask them not to increase the dose just to avoid side-effects or overdosing. If the patient is having inadequate pain relief after five days, we will increase the dose.

Regarding opioid-rotation; what method do you use to convert morphine to methadone?
We have a list of conversion ratios. We use this list for every patient.

Name: Dr W, prescriber of methadone

Title: MD

Date: (2019-12-03)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to MD as a prescribing doctor:

When do you consider initiating methadone-treatment in a patient?
- Upfront (as first-line opioid)?
- When failure on morphine? If yes- what morphine-dose?
- Any particular diagnosis?
- Nociceptive or neuropathic pain?
- Other situations?

It is very individual, whenever and in what stage the patient comes. We have seen the patient in MNJ, since we are admitted to MNJ cancer hospital, and many cancer patients come to us. Here in India, because lack of knowledge and low socioeconomic status, the patient comes late in the cancer-process of a metastatic stage and they will probably be having neuropathic pain. When as they have visited MNJ out-patient clinic many times I have seen patients coming with a lot of neuropathic pain apart from nociceptive pain. In such patients, we use methadone as a first-line opioid.

When it comes to diagnosis, any carcinoma of breast with metastasis or renal cell carcinoma. They can get toxicity of morphine because of accumulation of creatinine. Also, carcinoma of urinary bladder where the obstruction makes creatinine accumulate. Methadone is a good drug that is not excreted through the kidneys, it is excreted by the liver.

What special concerns do you have when prescribing methadone- any comorbidities or side-effects that are of special interest?
Patients who are having liver illness, cardiac problems – arrhythmias are contraindicated because of QT-prolongation and methadone might cause further arrhythmias. Methadone is being metabolized in the liver, and in patients with liver cirrhosis or other liver problems we will not be able to give methadone. Some patients will not be able to tolerate methadone, in such patients we also have to prescribe carefully. The first few days after initiating methadone, we will be following the patient and want them to be close because methadone has got high fatal toxicity index. Death due to methadone treatment usually occur during the first two weeks or more, so we have to watch them carefully. That is the special concern before methadone introduction.

Do you have concerns about addiction following the methadone prescription?
We give methadone in measured doses, any opioid can cause addiction. I haven't seen any patients who have been addicted to it. Even though, we have juvenile patients using methadone and since the past year I have been prescribing methadone. I have not yet seen any patient getting addicted to it. Maybe in the near future.

What are the requirements in the regulations when you prescribe methadone?
Prescriber should have the license to prescribe opioids, which I have, or it should be trough the pharmacy or the institution where it is being procured. Here we do this with the help of MNJ pharmacy.

Are there any contra-indications for methadone?
You shouldn't give methadone with midazolam, fluconazole is also contraindicated. With morphine you give adjuvance for neuropathic pain, like sodium valproate or amitriptyline. That is not being done when you are prescribing methadone. If affected liver metabolism, that is also a contraindication.

In what cases do you do base-line investigations?
Lab testing? (Which?)
ECG ?

We do baseline investigations in suspected cases, ECG and liver-function test.

What is the protocol you follow to initiate methadone?
Methadone is being initiated whenever you are switching from morphine to methadone. We use two kinds of procedures. One day regimen and three-day regimen. One day regimen I risky, I don't follow that. It is when you stop morphine and start methadone. I follow the three-day regimen.

There are certain formulations through which you will calculate how much methadone is required to give analgesic effect. Due to cross-tolerance of the drug we have to decrease 25% of that. One third of the calculated dose will be given first day, then two thirds on the second day and on the third day we will give the full calculated dose. Simultaneously, we will be decreasing the morphine dose. For the opioid naïve patient, we are starting with a low dose and do baseline investigations and investigating the patient´s previous medical history (cardiac events or liver impairment).

What makes you decide on pills or syrup?
I prefer syrup before pills. When you dose calculate, sometimes you will be have to dilute methadone. Syrup will be more handy in dosage, it is easy to dilute. Else, if you want to dilute pills you have to crush them and put them in normal saline.

How is the analgesic effect and dose-titration monitored? By whom (doctor, nurse)?
It is a coordination. We prescribe the medicine, and before prescription we take care of everything, and after that the nurse will be giving the instructions to the patient and I as doctor will also be giving instructions. If the patient has some kind of chest pain, drowsiness, or if you are having low respiratory rate then the patient or the caretaker should give us the information and we have to stop methadone. The information goes between the care giver, the care provider and the patient itself.

How do you decide on the amount of pills/milliliters you prescribe each time?
When the patient is in hospice, we prescribe daily. Two day-prescription when the patient is discharged, then the patient will have to go to MNJ. Less than 20 days. We want to have check on opioid toxicity and opioid dependency.

How much do you prescribe each time and how often can the patient refill?
They can come two days prior, depending on the amount of medicines they have. We have patients coming from 200-300 km away from Hyderabad centre so for those patients, we consider to give for 20-25 days and after that they can come.

What are your positive experiences of methadone over morphine?
It is a very good drug, potent drugs that can be given to patients who are having neuropathic pain apart from nociceptive pain. The thing is, the individual variation in large. It might be suitable for some patients.

Have you had any negative experiences from methadone-treatment? If so- what?
My personal patient experiences are of a patient with ampullary carcinoma who were in a lot of pain, he was receiving 60mg morphine IR four times daily. With that therapy he was not getting sufficient relief. At that time, we started him on injection ketamine, xylocard and we tried everything. Lastly, we introduced methadone and it had good effect. That was the first patient who received 20 mg three times daily. The patient was quite well, when he was experiencing break-through pain he got 5 mg methadone.

The other patient experience was a patient who was started on methadone and was not suitable with the therapy. We stopped because of inadequate pain-relief. We were using injection ketamine instead.

Methadone is a good drug that desensitises receptors. One patient was using 80mg morphine four times daily, the same patient was okay with 5mg methadone four times daily.

My negative experiences are that it is very individual how patients reacts to methadone. After giving methadone, some patients does not feel pain-relieved and I have, in those situations, had to switch back to morphine for the neuropathic pain and I had to add some adjuvance.

Do you give advice and instructions about over dosage and how to treat this to the patient?
Yes. We give advises for signs of over dosage, methadone should be kept without the reach of the patient. If the patient is taking the drug by his/herself it is important that the patient is conscious enough and understands what drug it is and what

complications can occur if he/she takes an overdose. It shouldn't be within the reach of children. If the patients experiences chest pain, drowsiness he/she should inform the care provider as early as possible.

Special symptoms of over-dosage are drowsiness, chest pain, numbness of one limb, vomiting, involuntary movements, opioid-toxicity. Opioid sensitivity can be the case sometimes, when we give them opioids for pain relief it affects the patient in the opposite way and cause pain. At that time we should tell the patient or the care-giver to contact us.

Regarding opioid-rotation; what method do you use to convert morphine to methadone?
Three-day regimen.

Name: Nurse N, at DPPC

Title: Nurse

Date: (2019-11-27)

Location for interview: Hospital

Translator: Yes

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to nurse at DPPC:

Do you feel confident in handling methadone?
Yes

What are your main concerns?
Those with liver problems may not be able to tolerate methadone, and it may be some changes in the ECG.

Have you had any negative experiences from methadone-treatment? If so- what?
No, I have not have any negative experiences.

What are your positive experiences of methadone over morphine?
After using morphine there are many patients whose pain has not subsided. However the amount of morphine, even though the amount of morphine has led to even over-dosage, some people's pain will not get reduced. For such people, methadone helps a lot.

What instructions do you give to patients and family about storing the drug at home?
First explain to the patient and their families how to use methadone, what is the dosage and what time intervals they should give. And also tell them to keep it away from children, store methadone in a place that is not accessible for children.

What instructions do you give patient and family about how to take methadone; number of pills/ml and daily doses? Maximum daily dose intake?
Depends on the pain score of the patient. Those who are already on morphine and are given methadone because they are not responding to morphine, so when they change from morphine to methadone there is a particular way it is changed as for the formula. I explain this to the patient.

Do you give any advice about symptoms of over-dosage and how to treat this?
She tells them that whenever they take methadone and experience anxiety, headache or palpitations they should immediately come and report it.

Name: Nurse P, at DPPC

Title: Nurse

Date: (2019-11-27)

Location for interview: Hospital

Translator: Yes

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to nurse at DPPC:

Do you feel confident in handling methadone?
Yes

What are your main concerns?
Whenever we are giving methadone syrup we explain to the patients that if any complaints, severe anxiety or confusion. First, we ask about past history – heart problems, erythema, and diabetes. If they don't have any problems, we give them the amount as prescribed by the doctor. We explain to the patient that if they have severe anxiety, confusion or any other problems to please inform the nurse at DPPC. We explain the doses. If any problems occur, the patient and the caregivers will come back to the physician. We give them methadone confidently.

As for concerns, my main concern is about some patients that are coming from a far away distance. They are not near the hospital and if they have any problems I inform them to immediately call me and inform me. We have a fear. We also inform the patients that methadone should be stored far away from the reach of children.

Have you had any negative experiences from methadone-treatment? If so- what?
Some patients have come to us and had worries about anxiety and confusion, drowsiness. I have experienced this in 2-3 patients.

What are your positive experiences of methadone over morphine?
Morphine dosage is a bit complicated, methadone is easier to explain dosage. Methadone gives better pain relief than morphine.

What instructions do you give to patients and family about storing the drug at home?
Kept far away in a safe place, should not be accessible for other than the patient particularly children. Methadone syrup is yellow in colour and children might mistake it for a drink.

What instructions do you give patient and family about how to take methadone; number of pills/ml and daily doses? Maximum daily dose intake?
I demonstrate the dosage to the patients with the help of syringes, putting 1 ml of methadone in a syringe. If the doctor prescribes 1 mg I put 1 ml in a syringe and demonstrate it to the patient that this is how they should take it.

Maximum daily dose intake depends on the prescribing doctor. Normally 0,5 mg but if the pain doesn't subside then the doctor increases it to 2,5 mg up to 5 mg. They give up to 20-30 ml for a month in their houses. Maximum suggested by the doctor is 5mg morning and evening. Always increases from a small dose to a big dose, it never starts with a big dose. If the pain subsides, it will be lowered. If the pain doesn't subside, the dosage gradually increases.

Do you give any advice about symptoms of over-dosage and how to treat this?
I advise the family that whenever there is an overdose the patient will sleep or the pulse will increase so the family should immediately bring the patient to the hospital. Blood pressure goes down. If any such sign, please bring the patient to the hospital.

Name: Nurse Y, at DPPC

Title: Nurse

Date: (2019-11-27)

Location for interview: Hospital

Translator: Yes

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to nurse at DPPC:

Do you feel confident in handling methadone?
Yes

What are your main concerns?
First of all you should do proper tests to ensure the patient is ready to take methadone. Electrolytes should be controlled, liver function test and ECG should be taken. If all these are controlled and okay, then methadone can be started. These are the main concerns.

Have you had any negative experiences from methadone-treatment? If so- what?
I have had negative experiences. Morphine is in a tablet form and methadone are in both a tablet and a liquid form. Sometimes the patients would take an injection form and they take a bit more or a bit less – they don't know how much to take. If it's a tablet form they know how much to take but if its an injection form they don't know how exactly to take the injection. These are my negative experiences. Some people have taken a wrong dosage because of the injection form.

What are your positive experiences of methadone over morphine?
Positive experiences is that those people who have taken morphine even 60mg or 120 mg daily without the pain subsiding experienced pain relief with methadone. For such people, methadone is working very well. Particularly in head- and neck cancers, methadone has worked very well in controlling the pain - much more than morphine.

What instructions do you give to patients and family about storing the drug at home?
I explain to the patient and the patient's caregivers that this is a dangerous drug and should not be in the wrong hands. If children or somebody else drink it there is a danger of those people dying, it should therefore be kept in a locked-in place. Only the patient should take the medication.

I also explain the proper dosage and also draw a diagram, showing the patient this is a very dangerous drug and can lead to death in some cases.

What instructions do you give patient and family about how to take methadone; number of pills/ml and daily doses? Maximum daily dose intake?
I go by the doctor´s prescription. If the doctors prescribe 10 mg and there are only 5 mg tablets available I explain to the patient to take two in the morning and two in the evening to make it 10 mg. If it is tablet it is easy to explain to the patients. If it is in syrup form it is easy for the doctors to write but it becomes much more difficult for the nurses to explain to the patient how to take the syrup. If it is written 12mg I put 1 ml of syrup and 4 ml of water in it, mixed it and give it to the patient.

As for maximum daily dose intake, I go by the prescription of the doctor. If its three times daily, then the maximum dose is three times daily. If they are also prescribed rescue doses of morphine, this can also be given.

Do you give any advice about symptoms of over-dosage and how to treat this?
Drowsiness, confusion and delirium, talking in a confused an incoherent way. Morphine generally comes out in the urine, but methadone stays in the blood and can lead to side-effects. Heavy dosage may result in death also.

Generally they are giving methadone to those living close to the hospital. In cases of over-dosage, our home care teams can follow up. I advise the patients to come to the hospital immediately. Within a week after methadone introduction we have a phone follow-up with the patient. We have to ring them up on a daily basis.

Name: Nurse S, at the Hospice

Title: Nurse

Date: (2019-11-27)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting.

Questions to nurse at the Hospice:

Do you feel confident in handling methadone?
Yes I do.

What are your main concerns?
There is a lot of education required in starting methadone. I can frankly say that a lot of our team, a lot of members in the society, a lot of doctors and nurses too, doesn't have a background of methadone even though they see a lot of patients in hospice and MNJ. Even though, they don't have a lot of information.

Since day one of implementing methadone we had a lot of workshops and information and a lot of discussions in the team about how confident we felt in starting methadone and what kind of approach do you require. So, in that situation, we were new to methadone and didn't know anything. Later on, discussion gathering and lectures that gave us information earlier have not been happening because of a large staff so that was a long time ago. Two years ago, when we started methadone, we had a lesser number of team but now it has expanded and there is no right person to handle methadone and have an overall view as a central team. There should be somebody looking on all the aspects, both in home care or in hospice, and looking after if we are doing what we are thought. You have to see for the toxic effect of methadone. That kind of education I would require. I keep telling our team to have more discussions about methadone, once you face any death just because of methadone. Then people start talking about how we can improve, but we should talk about this beforehand so that everybody has information about "dos and donts" of methadone and how to store it.

Have you had any negative experiences from methadone-treatment? If so- what?
It was information about a family that was given 10 ml syringe loaded with methadone, 1 ml = 5 mg. If they are to administer it three times a day they either take a spoon or they drop from the syringe and apply. One day, all of a sudden, the family was not so interested in doing that procedure and they didn't want to waste time so they pushed the syringe and gave 2-3 ml at a time. After that happened, we had a discussion again, and we thought of not disposing it like that and use a dropper instead.

A lot of families were using a plastic bottle, a disposal plastic bottle which should not be used for a long time, for storing methadone and they were using it for more than a week or ten days. We thought that was not a safe idea and we prefer glass bottles that would be safer than plastic bottles.

This is India, we try to go in the cheapest way and we therefore can't put a lot of pressure on the families to spend money on these things. Sometimes we took a sample collection bottle, with a white cap, with a lid that can be closed and it happened that it fell down.

The family has kept methadone in a bottle but not in the correct place, they kept it in the freezer. A child thought it was a cool drink and drank a little from the bottle. With this experience we are now telling the families not to do this.

What are your positive experiences of methadone over morphine?
There were some 6-7 cases of patients with severe uncontrolled neuropathic pain that were having a good pain relief with methadone. There are a few patients who are unable to open their mouths, cases of buccal mucositis in H&N-cancers, and it is then more easy to administer methadone buccally and it helped a lot. Many patients with vomiting have been converted to methadone and it helped them.

What instructions do you give to patients and family about storing the drug at home?
When I am working in home care I prefer, because I've been here since the last twelve years but recently I've been to Canada saw them using information sheets, to write a note in our local language with information regarding where they should keep the methadone. It should be kept somewhere on the top, not close to the kids, dark place, clean container, use a dropper or a syringe, take a small amount of solution and do not waste it.

We tell most of the family members that if you have a lot of giddiness or if you are too drowsy, stop and inform us. Maybe they do not know about that and feel like if the pain is uncontrolled they just misunderstand the information, its not like the MNJ people are not giving the information, but they do not look at the whole aspect when they go home. They only remember some points and they start implementing it. Some also have the feeling that it is a drug which is a sedative and that we are giving the drug for a sedation, that kind of information is a misunderstanding. Even though we write the information in a sheet that is for pain. I have given it to 2-3 patients in home care. Whenever they have a doubt about it they go through that list again and again. When I come to visit them I try to review them about methadone, and they start telling me the information. I feel, the patients should even in their sleep feel clear about it.

What instructions do you give patient and family about how to take methadone; number of pills/ml and daily doses? Maximum daily dose intake?
What Dr Gayatri have suggested is that: Give it in the prescribed time. We give a written format to the family with a clock symbol and the timings on a chart. If the patient is not able to take the drug orally it can also be kept in the buccal. When the patient goes home, things may change, and the patient may become drowsy and the condition becomes worse and they can't take their medicines orally. In these cases they often stop the medicine, but instead they can just administer it buccally. That's what we prefer.

Maximum dose intake it whatever the doctor has prescribed. We start with once daily and increase to two times a day and then three times a day. If the patient is still having a lot of pain, and for the breakthrough, we use oral morphine, or else we go for the low dose of methadone as SOS-dose. We do this very rarely though since we are not suggesting methadone to be taken more frequently - because we haven't learned about that. Dr Gayatri have also suggested methadone can be taken for breakthrough pain but we are not preferring that, for our understanding we go in the same way. Maybe in the future, methadone can be taken even for breakthrough pain.

Do you give any advice about symptoms of over-dosage and how to treat this?
We do, in a written format. On the time of discharge, even for patients admitted in the hospital, we do not educate them much. When they go home, we give them a discharge summary in a written format, it explains whatever toxic effects the patients might experience and what the family should look for. If they find such problems they must inform the team and the medication should not be given for ten days. After ten days they come back and meanwhile if there is any problem they have to inform us. If the patient passes away we tell the attendants to return it to us instead of discharging it somewhere. The side-effects will also be thought to them. When we administer the medicine, we tell them it is a medicine for pain so that they don't have any misunderstandings and after they have taken this they might become drowsy. To prevent that, we tell them that this is only for pain.

There is a very good pain relief with methadone.

Name: Pharmacist S, at the hospital

Title: Pharmacist

Date: (2019-11-27)

Location for interview: Hospital

Translator: Yes

Content of interview: Experiences in the use of methadone in a low-resource setting

Questions to nurse at Pharmacist:

How do you maintain the stocking?
We keep them in 24 degrees Celsius. We keep them locked-in, in their package (original strip).

What formulations of methadone do you have? And what strengths? What is the price?
Tablet and syrup. Tablet strength 5 mg. Syrup strength 5 mg per 1 ml.

Price per tablet: 3 rupees 37 pence.
Price per bottle of syrup (150 ml): 750 rupees.

How much do you dispense each time and how often can the patient refill?
Depends on doctors' prescription. We dispense only with the help of doctor´s prescription. The doctors can prescribe any amount. The patients first consult the doctor, then only if the patient is getting a prescription they come and collect the tablets from the pharmacy.

Do you have any concerns about methadone?
It is the duty of consulting doctor. No concerns. MNJ has had methadone since April 2017.

Name: Administrator V

Title: Hospital administrator

Date: (2019-11-30)

Location for interview: Hospital

Translator: No

Content of interview: Experiences in the use of methadone in a low-resource setting

How do you get the license to procure methadone?
The license to procure methadone in MNJ is as per the government order released by government of India, in the year 2015. The amended rule says that any government hospital can apply for a license called recognized medical institution license, its called RMI.

The government order also says that any government hospital which is working directly under the state government is a deemed RMI, I mean the drug control authority which gives us the recognition or the license need not give us certificate saying you have an RMI, it is a deemed RMI. That's one part of it.

The second thing is to get the annual counter of this methadone, whatever formulations we need for our patients which we use in DPPC. For example, in the year 2017 when we first got the license to procure stock and dispense methadone, it says that you can procure for the year 2017 22 000 5 mg tablets of methadone and 150 bottles of 5mg/1ml methadone syrup. So, that is how we got that permission. Because that stock had come for the last two years we didn't apply any stock again for the year of 2018 and 2019. For the year of 2020, we have recently applied to the drug control authority along with other opioids. We applied

with a requirement and showed them which patients we have seen in the previous years and this would be our consumption so kindly give us permission to procure methadone.

Where do you purchase methadone?
As per the hospital protocol. So, whenever the drug control authority gives us the license it says that you can purchase this number of quantity, X number of bottles of syrup or Y number of tablets. We then have to approach the hospital purchase section, saying that we need X bottles and Y tablets of methadone, and they approach certain pharmaceutical companies and they call for the quotations. I mean, they call X company and Y company and all the companies that have the license to give us methadone. If they have the license, they can participate in the tender and they can submit the quotation. The hospital will sit as the committee consisting of four to five people, which includes the head of the department, head of the hospital, administrator officer and the resident medical officer. The sit and open the quotations and look into which company has quoted the least price. Then that company gets the chance to send methadone to our hospital.

There are many pharmaceutical companies involved in the process. Recently I came to know that there is no tough competition for one pharmaceutical company and only one pharmaceutical company in India manufactures and gives methadone. So for now, that company doesn't have any tough competition. In future it may come.