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Use of methadone as an alternative to morphine for chronic pain management: a noninferiority retrospective observational study

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Abstract

Introduction: Chronic pain causes disability and is prevalent in the general population. Opioids are a part of a multimodal strategy for pain management. Methadone, a cheap and long-acting synthetic opioid, may represent an option for those who have limited access to the aforementioned class of analgesics. We aimed to provide a real-world evidence for the analgesic use of methadone, compared with morphine.

Methods: We conducted a noninferiority, retrospective observational single center study of patients with chronic pain, managed with either methadone or morphine at an outpatient specialized clinic. We extracted data from the electronic health records of patients who underwent an active treatment between August 2012 and January 2020 and were examined for at least 2 consecutive medical visits, after the administration of one of the aforementioned drugs. Data were analyzed using a generalized additive model with random-effects mixed linear method to account for the individual-related, time-related, and drug-related variations. The numeric verbal scale (0–10) was used to assess the pain severity.

Results: From the database of 3373 patients, we included 262 patients (175 methadone and 87 morphine). In an unadjusted analysis, methadone was superior to morphine, and the mean worst pain was 0.86 points lower (95% confidence interval, −1.29 to −0.43). Moreover, methadone was superior to morphine in the adjusted analysis, with the worst pain mean being 1.24 points lower. This provided evidence for the noninferiority of methadone than morphine.

Conclusion: Methadone was superior to morphine in a 20% noninferiority margin for reducing worst pain.

Keywords: Opioid analgesics, Methadone, Morphine, Chronic pain, Noninferiority trials

1. Introduction

Chronic pain is a common cause of severe disability. Approximately 1 in every 5 American adults, or 30 million people, experience chronic pain, thereby representing a substantial loss to the economy. The use of opioid analgesics is ubiquitous in cancer pain. However, there are conflicting reports for chronic noncancer pain. Some studies have reported on good pain relief with the long-term use of opioids, occasionally with functional improvement. Considering the commonly selected samples in multidisciplinary pain control programs, other studies conclude that chronic opioid therapy exacerbates psychological distress, impairs cognition, and worsens the outcomes.[4,31]

Finally, the use of opioid analgesics has gained attention in lay media as well as in scientific publications. This can be attributed to the opioid crisis in several countries and, in particular, in the United States. Nonetheless, we cannot underestimate the proportion of people worldwide who still do not have adequate access to the aforementioned essential analgesics.[30] Methadone may play an important role in increasing the access to opioids.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Methadone is a long-acting synthetic and easily manufactured opioid, first developed during World War II. It is commonly considered a cornerstone in the treatment of opioid addicts. However, it is being increasingly used for its analgesic properties.[6,25] Methadone is a more affordable option than other long-acting opioids. Therefore, its use may be particularly appealing in low-income populations or developing countries, such as Africa and Latin America.[6] Its unique analgesic properties prevent monoamine reuptake in the periaqueductal gray region of the brain and inhibit presynaptic N-methyl-D-aspartate antagonist (NMDA) receptors, in addition to its highly potent opioid receptors agonist actions. The aforementioned special features enable methadone to modulate pain stimuli propagation to reduce the development of hyperalgesia and opioid tolerance.[25] Furthermore, the NMDA activity might increase its usefulness in the management of intractable neuropathic pain.[32]

However, prescribing methadone analgesic is challenging owing to the wide interindividual variability in its pharmacokinetics. This characteristic makes it difficult to predict the relationship between the dose, plasma concentrations, and pharmacologic effects.[4] By contrast, morphine is considered a prototype of an opioid that was first isolated in 1803. It is classified as a strong opioid analgesic, similar to methadone, used for the management of acute and chronic pain of moderate to severe intensity.[9] However, the use of morphine as the reference standard opioid for the treatment of severe chronic pain is controversial.[3]

Few studies have compared methadone and morphine for the management of chronic pain in patients treated at an outpatient specialized clinic. In addition, no study has compared these strong opioids in a real-world clinical setting.

Studies with real-world data (RWD) include information from prospective or retrospective observational studies. Unlike controlled trials, patients in the aforementioned studies are treated according to the local clinical characteristics and preferences. In addition, evidences extracted from the RWD represent a situation closer to the procedures adopted in clinical practice. Thus, they comprise interferences that are often not a part of controlled and randomized studies, such as the existence of comorbidities, concomitant treatments, lack of data, discontinuities, and low adherence.[29] Retrospective studies are potentially valuable for filling gaps in scientific evidence, particularly regarding safety information and postmarketing effectiveness.[10]

We aimed to provide real-world evidence for the analgesic use of methadone, compared with morphine. Our primary objective was to evaluate pain improvement in outpatients diagnosed with chronic pain of various etiologies who were administered morphine or methadone. We also intended to evaluate the incidence of analgesic-associated adverse events. We hypothesized that analgesic effects of methadone in a real-life setting are not inferior to that of morphine.

2. Methods

Our study was approved by the institution's ethical committee in human research, which waived the need for patient's informed consent because it was a retrospective study and all data were unidentified.

2.1. Study design and population

We conducted a noninferiority, retrospective observational single center study comprising patients with chronic pain, managed with methadone or morphine at an outpatient specialized Pain Management and Palliative Care Unit of the Teaching Hospital of Botucatu Medical School—UNESP, Brazil. The report is in accordance to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12]

We obtained the electronic health records from October 2019 to March 2020, and included those who underwent active treatment between August 2012 and January 2020, during which the records were documented in the institution. These records comprised a specific pain form that was searched during data collection. We excluded patients with incomplete medical records.

The inclusion criteria were as follows: age ≥18 years, diagnosed with chronic pain (lasting longer than 6 months), under treatment with methadone (Mytedom; Cristália Produtos Químicos Farmacêuticos Ltda, Brazil) or morphine (Dimorf; Cristália Produtos Químicos Farmacêuticos Ltda, Brazil), no concomitant treatment with other opioids, and inspected for at least 2 consecutive medical visits after the administration of one of the studied analgesics (**Fig. 1**). Patients who were administered analgesic interventions, unable to inform their pain score, or using other opioids were excluded. All medical visits were documented for analysis purposes. Only those patients who adhered to the prescribed oral doses of methadone or morphine, according to the need for treatment of each patient and clinical condition, were included.

Both analgesic drugs are pure μ-opioid agonists, and their maximum doses (ceiling effect) have not been established in existing literature. Moreover, their use is extremely flexible, depending on the individualized demand of the patient.[36] We recorded the dose used for each drug.

Other adjuvant analgesics, including paracetamol or tricyclic antidepressants, could be simultaneously used. Laxatives were routinely prescribed *at libidum* to all participants with a prescribed opioid at the clinic. All medications in use were recorded. Patients who clearly did not adhere to treatment were not included in the study.

2.2. Outcomes

The primary outcome for effectiveness were repeated measures of the worst pain score, measured using an 11-point numeric verbal scale, ranging from 0 to 10 (0 = the absence of pain and 10 = the worst imaginable pain). We analyzed data from the worst pain experienced by the patients. Secondary effectiveness outcomes included the performance status measured by the Karnofsky Performance Status and the occurrence of side effects registered in the medical records.[37] We assessed the effectiveness outcomes in prespecified subgroups of patients. The patients were categorized by their sex, age, and pain origin classification

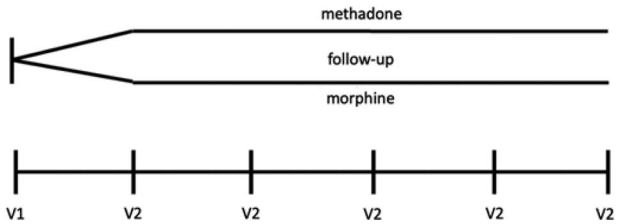

Figure 1. Study timeline.

(nociceptive, neuropathic, mixed, and nociplastic pain) in accordance to the diagnosis.[41] While fibromyalgia and migraine diagnosis were categorized as nociplastic pain, lumbar pain with sciatic irradiation was categorized as mixed pain.[15] We also evaluated the doses of opioids administered.

2.3. Statistical analyses

Baseline characteristics of the study population and safety were reported using descriptive statistics. We conducted the Fisher exact test, *t* test, or Wilcoxon–Mann–Whitney when appropriate to test the hypothesis of differences between the groups. To compare the effectiveness of methadone and morphine in pain management, we used a noninferiority hypothesis. The design used had parallel groups, and the proportion of participants was the primary variable, with a 20% margin of noninferiority in mean pain improvement, at least 1 month after the last medical appointment. Therefore, we calculated the sample size based on a parallel design with 2 samples and a noninferiority test for means, with a 20% margin of noninferiority, a power of 80%, and an alpha error of 0.05.

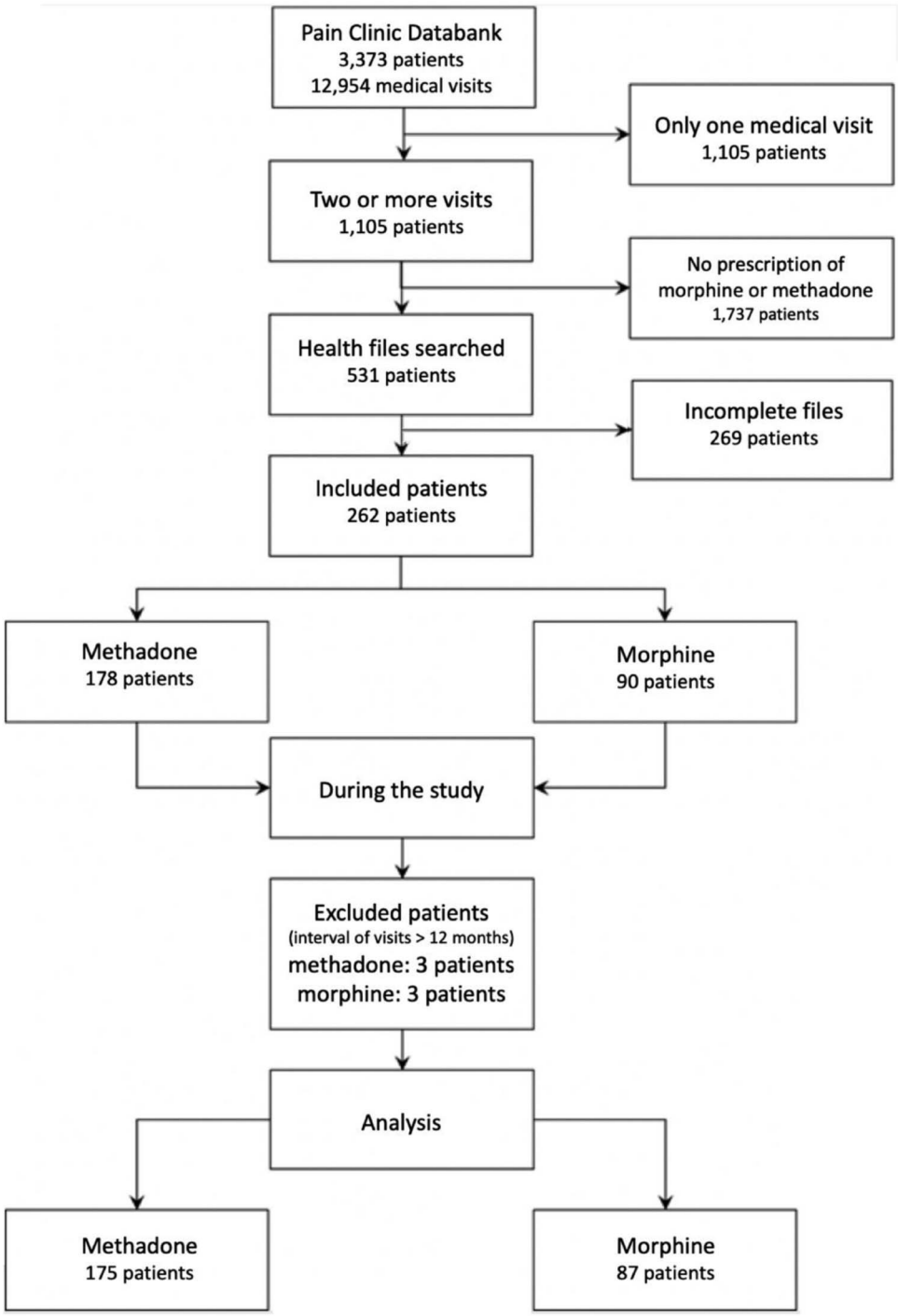

Figure 2. Flow diagram depicting patient selection.

Data collected after 365 days were excluded. For graphical reasons, we converted the dates to bin intervals of 40 days. We plotted both error plots and predicted the continuous data using locally weighted scatterplot smoothing. We analyzed the longitudinal data using a generalized additive model (GAM) with integrated smoothness estimation using the function GAM from the mgcv package for R and the random-effects mixed linear method (read the Statistical Analysis Code for more details) to account for the individual-related, time-related, and drug-related variations.[42] We performed the analysis in the entire sample using the following formula: age + drug + pain classification + gender + random effects (time and patient identity). A secondary analysis (using data obtained after 120 days of inclusion) was performed to exclude the possible effects of outliers in the third time bin (79–119 days).

3. Results

3.1. Sample overall description

The database included 3373 patients, of whom 531 were administered methadone or morphine. They had been registered for at least 2 consecutive medical appointments, with an interval of up to 12 months, which reflected the time of continuous use of each analgesic. We included only those patients who had consumed the medications as directed by the assistant physician.

Of the selected patients, 262 met the inclusion criteria. Methadone or morphine was used by 175 and 87 patients, respectively (**Fig. 2**). The mean age of patients consuming methadone and morphine was 62.1 years and 55.5 years, respectively. Most patients were female (62.7%). Nonetheless, the distribution was more equal for those consuming morphine. **Table 1** summarizes the patient anthropometrics and pain classifications.

3.2. Primary outcome

In an unadjusted analysis, methadone was superior to morphine, and the mean worst pain was 0.86 lower (95% CI −1.29 to −0.43). In our adjusted analysis, methadone was superior to morphine, and the worst pain mean was 1.24 points lower (**Fig. 3** and **Table 2**). However, we noticed a high effect in the third time bin. Best pain scores at the first 40 days bin were 4.1 ± 2.8 and 3.7 ± 2.6 for morphine and methadone, respectively (results not shown). We then excluded data from the first 120 days to determine whether methadone performed worse than morphine, as a worst-case scenario. Methadone predicted a lower mean of worst pain even in the second analysis (**Table 3**). Nonetheless, the difference was statistically insignificant. The −0.3 point in an 11-point (0–10) verbal scale difference is clinically meaningless. Thus, with an absolute confidence interval (−0.88 to 0.66) not crossing the proposed noninferiority margin (20% of 8.3 would be 1.66) even in the worst-case scenario, this study provides evidence in favor of the noninferiority of methadone.

3.3. Secondary outcomes

There were few reports in the medical records on the occurrence of opioid use–related adverse events. Therefore, we could not conduct statistical tests for comparing between the 2 groups. Nausea was the most frequently registered side effect (**Table 4**).

During the visits, the average of the Karnofsky scale was stable, oscillating between 75 and 82 in the groups (data not shown). The mean difference in the scores (between the final and baseline treatment per treatment) was −0.960 and −0.500 for morphine and methadone users, respectively. The *P* value was 0.814, indicating no difference between the 2 groups (**Table 5**).

Although methadone doses were extremely stable during the follow-up, morphine doses were more variable and even decreased at the end of a year of follow-up (**Table 1** and **Fig. 4**).

4. Discussion

Few studies have compared between methadone and morphine for the treatment of opioid use disorder[24] as well in the perioperative setting.[23] However, there are fewer studies comparing the chronic use of these opioids. Moreover, none of them focused on a real-life setting.

Table 1

Patient anthropometrics, median of opioid consumption, and pain origin, in accordance to the diagnosis.

Variable	Methadone (n = 175)	Morphine (n = 87)	Total (n = 262)
Gender* n (%)			
Female	116 (66.3%)	49 (55.7%)	165 (62.7%)
Male	59 (33.7%)	38 (44.3%)	98 (37.3%)
Age†	62.1 (±15.5)	55.5 (±12.02)	59.2 (±14.9)
Opioid consumption‡	12.6 (±13.3)	47.4 (±57.6)	—
Cancer-related pain§	17 (9.7%)	42 (48.2%)	59 (22.5%)
Pain origin‖			
Nociceptive¶	53 (30.2%)	51 (56.0%)	104 (39.7%)
Neuropathic#	41 (23.4%)	16 (18.3%)	57 (21.7%)
Mixed**	61 (34.8%)	17 (19%)	78 (29.8%)
Nociplastic††	19 (10.8%)	2 (2.2%)	21 (8%.0%)
Missing data‡‡	1 (0.8%)	1 (4.5%)	2 (0%.8%)

* $P = 0.106$ (Fisher test).
† Mean (standard deviation), $P = 0.0002$ (*t* test).
‡ Mean during the entire follow-up period (standard deviation), value expressed in mg.
§ $P < 0.0001$ (Fisher test).
‖ Mean; mixed pain = neuropathic and nociceptive components, *P* values (Fisher test).
¶ $P = <0.0001$.
# $P = 0.42$.
** $P = 0.014$.
†† $P = 0.015$.
‡‡ $P = 1$.

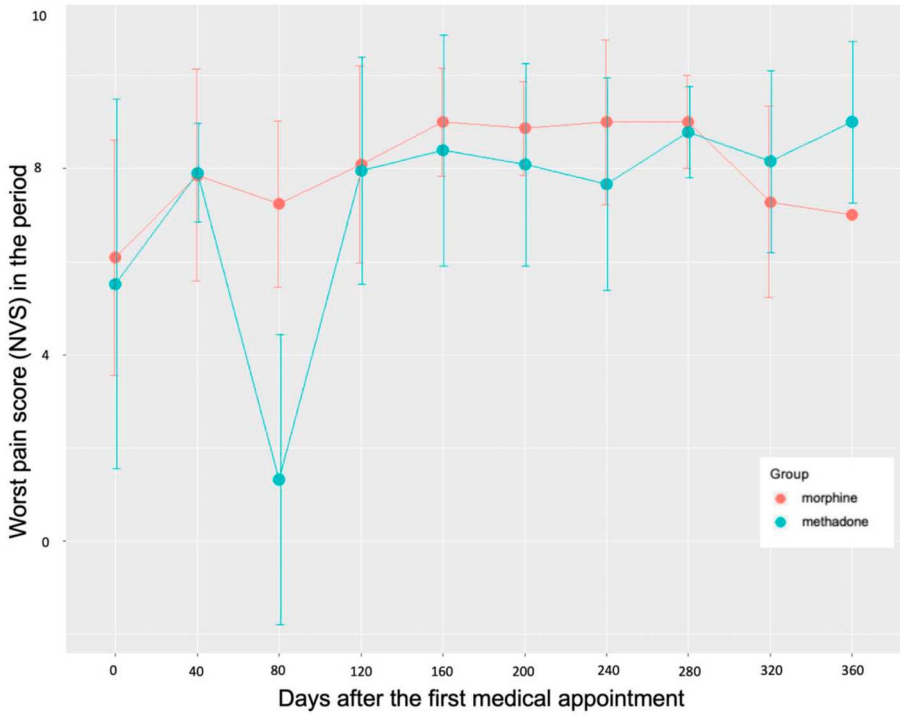

Figure 3. Numeric verbal scale (NVS scores 0–10) scores for worst pain in patients consuming methadone or morphine during the follow-up.

Of the total 3373 health records evaluated, only 262 patients (7.76%) fulfilled the inclusion criteria. This low sample size may reflect the difficulty to obtain RWD. This is because numerous clinical records are incomplete and several important information may be missing. We only considered reliable data obtained from the health records for analysis, thus ensuring the patients presented adequate compliance to the prescribed medicines. Moreover, we adopted a judicious inclusion criteria that sought to remove interferences from other pharmacological or nonpharmacological treatments that could alter the pain pattern.

The results and conclusions of studies including RWD currently represent strong evidences. Few years ago, the U.S. Food and Drug Administration (FDA) released a draft guidance on the use of real-world evidence to support regulatory decision making for medical devices. The FDA guidance defines RWD as data collected from different sources, including retrospective studies and electronic health records.[29]

The mean age of our selected patients was quite similar to the age of individuals included in a population-based chronic pain survey, conducted at the city where the pain clinic was located. While the mean age of the included patients was 59.2 years, 55.3% of those with chronic pain were aged between 40 years and 69 years. Chronic pain was more prevalent in women (72.3%) in a population-based study, compared with 62.7% in this study.[2]

The patients who received methadone presented a higher mean age than those who received morphine ($P = 0.0002$). This

Table 2

Mixed-effects model summary to predict worst pain in the entire year.

Effect	Estimate	*P*
Intercept	8.9	<0.0001
Age (per year)	−0.01	0.24
Gender		
Female	Ref	
Male	−0.76	0.0005
Opioid		
Morphine	Ref	
Methadone	−1.24	0.0014
Pain classification		
Nociceptive	Ref	
Neuropathic	+0.41	0.14
Mixed	+0.63	0.015
Nociplastic	+1.88	<0.0001
Missing data	+1.16	<0.28
Random effects (time, id*)	—	<0.0001

* id: subject. Generalized additive model with integrated smoothness estimation.

Table 3

Mixed-effects model summary to predict worst pain in the subset after 120 days.

Effect	Estimate	*P*
Intercept	9.11	<0.0001
Age (per year)	−0.009	0.35
Gender		
Female	Ref	
Male	+0.42	0.12
Drug		
Morphine	Ref	
Methadone	−0.31	0.32
Pain classification		
Nociceptive	Ref	
Neuropathic	−0.84	0.02
Mixed	−0.46	0.16
Nociplastic	+1.04	0.03
Missing data	−2.45	0.19
Random effects (time, id*)	—	0.07

* id: subject. Generalized additive model with integrated smoothness estimation.

Table 4

Side effects of opioid use registered in the health records.

Side effect	Methadone (n = 175)	Morphine (n = 87)	Total (n = 262)
Nausea	17	6	23
Somnolence	6	5	11
Intestinal constipation	5	3	8
Vomit	4	2	6
Mental confusion/delirium	1	4	5
Pruritus	1	0	1
Total	34 (19.4%)	20 (23.9%)	54 (20.6%)

may be attributed to the characteristics of experienced pain, particularly neuropathic pain. The prevalence of neuropathic pain is higher in women and increases with age.[5] Furthermore, methadone may be particularly useful in the neuropathic and mixed pain management.[32] Methadone does not have active metabolites, and may be beneficial for those with renal impairments, prevalent in the elderly population.[25,26] The aforementioned factors might have influenced the prescription for methadone. Morphine and methadone were the only strong opioids free of charge at the above-mentioned government-sponsored pain clinic.

Nociceptive pain was more prevalent in patients who received morphine. By contrast, mixed and nociplastic pain were more prevalent among methadone users. Despite the equal distribution of patients with neuropathic pain in both groups, the proportion was slightly higher among methadone users. Our findings are similar to Latina et al. who reported that while 45% of the patients attending a pain clinic presented with musculoskeletal and visceral pain (ie, nociceptive pain), 20.9% presented with neuropathic pain.[27] Pure nociceptive pain may be extremely rare.[38] However, it is exceedingly common in cancer pain and musculoskeletal pain.

In cancer pain, opiophobia and morphine avoidance are less common.[30] This may explain the prevalence of nociceptive pain in patients consuming morphine, who presented with larger instances of cancer-related pain. Furthermore, as opioid use disorder is not a prevalent problem in Brazil,[30] there is no social stigma associated with methadone because it is not used in the treatment of heroin addicts, unlike other countries.[35] The aforementioned facts may facilitate the prescription of methadone for non–cancer-related pain by the assistant physician, despite the efficacy of this opioid for cancer-related neuropathic pain.[20]

Our primary hypothesis was that methadone was not inferior to morphine during chronic pain management. Interestingly, methadone was superior to its comparator analgesic, however, without any clinical relevance. A reduction of approximately 2 points in the pain score is necessary to represent a clinically relevant difference.[14] We observed a 1.2-point pain score reduction in methadone users, compared with morphine users.

Table 5

Evaluating the difference observed in the Karnofsky Scale: during the first medical appointment and after the introduction of studied analgesics.

Δ Karnofsky scale	Methadone (n = 113)	Morphine (n = 52)	*P*
Mean	−0.50	−0.96	0.814

t test.

Methadone presents several advantages over morphine in the treatment of cancer pain. However, a consensus has not yet been achieved.[1,13,39] It has a lower cost, high oral bioavailability, long half-life, no active metabolites, and a perception of benefits in challenging pain situations.[17] Therefore, 9.7% of the methadone users in our study experienced cancer pain. However, physicians should carefully prescribe the drug because of its varied pharmacokinetic and pharmacodynamic properties, interindividual variations with unpredictable occurrence of side effects, and incomplete cross tolerance with other μ opioids.[1,13,17,28]

Methadone usage has not achieved a consensus even in chronic noncancer pain. Moreover, it raises concerns, particularly after the development of recreational opioid crises in some countries.[4,30] There is little evidence for its benefits and a strong concern over its safety.[7,19] However, in this study, the occurrence of side effects was extremely low, with nausea being the most frequent one. We did not record any life-threatening events, including respiratory depression because of overdose or opioid addiction.

Raja et al. reported that constipation, nausea, drowsiness, and loss of appetite are commonly observed on the use of morphine or methadone for the management of postherpetic neuralgia.[33] According to Kalso et al.[22] constipation, nausea, and somnolence or sedation are the most frequent side effects during opioid use for noncancer pain management. Opioid side effects in patients with chronic noncancer pain may increase their morbidity and mortality, affect the quality of life, and lead to the discontinuation of chronic opioid therapy.[7,8] We did not investigate the discontinuation rate related to opioid side effects.

Adverse events occur at all dose ranges, despite an increase in their frequency with regular opioid use, higher doses, long-term therapy, polypharmacy, and decreased renal or hepatic function.[11,16,34] We did not investigate the relation between the side effects and the time and dose of opioid use. Methadone doses were much more stable over time than morphine, which may represent superiority over morphine. Henry et al. observed that dose escalation during the first year of long-term opioid therapy for chronic pain occurs in 9% of the patients, which in turn tends to be associated with higher risks of substance use disorders.[21]

The overall dose of both opioids in our study was low and might have influenced the low incidence of side effects, including the life-threatening ones. Clinical guidelines tend to define ≥200 mg morphine per day or equivalent as a high dose, based on expert opinion and commonly studied doses in medical literature.[11,16] In this study, the opioid median doses were significantly below the aforementioned dose. Moreover, Trofimovitch et al.[40] mentioned that 11.18 mg methadone is equivalent to 47.4 mg morphine. The mean methadone dose registered in our study was 12.6 mg.

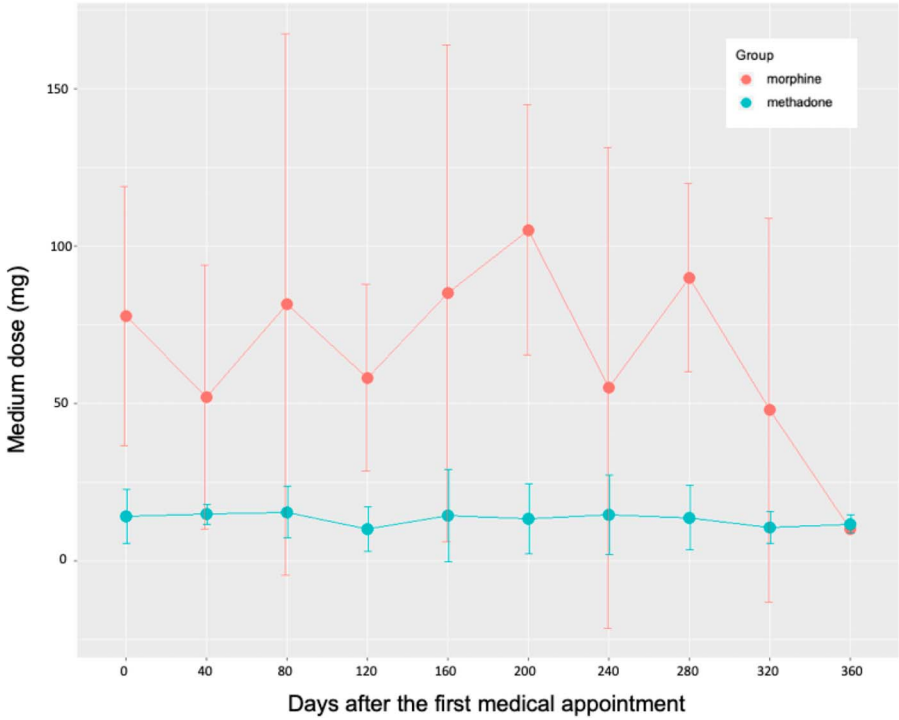

Figure 4. Methadone and morphine dose variation during the follow-up. Opioids were prescribed on day "0."

Physicians should consider the performance status while prescribing opioids for chronic pain. Poor performance status in patients with cancer is often associated with higher symptom burden, predominantly pain, which may demand higher opioid use.[18] In this study, despite the higher frequency of cancer pain in the morphine group, it did not affect the analgesic efficacy. This can be attributed to the lack of difference in the performance status between methadone and morphine, as measured by the Karnofsky score.

There are limited data supporting the long-term use of opioids for noncancer pain relief. Moreover, we do not advise the undiscerning prescription of opioids. However, we believe that patients with chronic noncancer pain, who are likely to benefit from potent opioids, should not be prevented from obtaining this treatment. Therefore, careful selection of patients, meticulous prescriptions, and monitoring of protocols should be enforced. Guidelines on long-term opioid therapy recommend a single physician to conduct the medication management. All patients must undergo a clinical risk evaluation. The treatment agreements must be signed, and physicians must perform periodic monitoring, urine drug screening, and the documentation of treatment in the medical records.[8] Opioids prescription should be considered for patients with cancer and moderate to severe pain because they are the mainstay of analgesic therapy.[13]

Despite ensuring the precise documentation of all data available in the health records, the study had few limitations. Our findings were observational in nature, and we failed to establish a causation. Methadone is still considered an analgesic that should only be prescribed by physicians with an experience and expertise in its use.[13] This necessitates further research to better understand the precise role of methadone in chronic pain management.

In conclusion, methadone was superior to morphine in a 20% noninferiority margin in reducing worst pain, both in adjusted and unadjusted analysis. Side effects rarely occurred, and there were no reports of life-threatening events. Methadone users presented a more stable state during the investigation.

Disclosures

The authors have no conflict of interest to declare.

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