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PERMANYER

DOLOR. 2016;31:29-36

# Cognitive disorders in patients receiving methadone: A descriptive study in a teaching hospital

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## *ABSTRACT*

The need for pain treatment based on opioid analgesics increases, but their use is often limited by side effects, including cognitive disorders. It is important to evaluate cognitive status during opioid treatment. A retrospective review of methadone prescriptions over 17 months in a university hospital database was followed by a medical records review of 74 patients, of which 73% were aged 60 years or older, 74% had chronic clinical conditions, and 64% had been admitted for pain. The mean initial pain intensity was 4.8/10 (SD: 3.3), while the mean intensity after treatment was 1.8/10 (SD: 2.0). The most frequent type of pain was oncologic (49%), and prescriptions were generated by specialists affiliated to pain services (75%). A quarter of patients treated with methadone experienced cognitive disorders; this was more common in men, patients aged 60 years and older, and those exposed to benzodiazepines and higher doses of methadone. Optimal use of nonsteroidal anti-inflammatory drugs and other analgesics is essential to decrease the opioid dose and limit the use of benzodiazepines. Patients undergoing methadone therapy should be assessed for cognitive function before starting treatment and at the end of treatment. (DOLOR. 2016;31:29-36)

***Key words:*** *Benzodiazepine. Cognitive. Methadone. Pain. Screening.*

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## *RESUMEN*

La necesidad del tratamiento del dolor basado en analgésicos opioides aumenta, pero su uso es limitado por sus efectos secundarios, incluyendo trastornos cognitivos. Es importante evaluar el estado cognitivo durante el tratamiento con opioides. Una revisión retrospectiva de prescripciones de metadona, durante 17 meses, en la base de datos de un hospital universitario, fue seguido de informes médicos a 74 pacientes, de los cuales el 73% tenían 60 años de edad, el 74% enfermedades clínicas crónicas y el 64% fueron ingresados por dolor. La intensidad media inicial del dolor era de 4,8/10 (SD: 3,3), mientras que la intensidad media del dolor después del tratamiento era de 1,8/10 (SD: 2,0). El tipo de dolor más frecuente era el dolor oncológico (49%), y las prescripciones fueron hechas por especialistas vinculados a los servicios de dolor (75%). Un cuarto de los pacientes tratados con metadona experimentaron trastornos cognitivos; esto era más común en los hombres, en los pacientes con 60 años de edad y en aquellos expuestos a benzodiazepinas y a altas dosis de metadona. Un uso idóneo de fármacos antiinflamatorios no esteroides y otros analgésicos son esenciales para diminuir la dosis de opioides y limitar el uso de benzodiazepinas. Las funciones cognitivas de los pacientes sometidos a una terapia con metadona, deberían ser evaluadas antes de empezar el tratamiento y al final del mismo.

***Palabras clave:*** *Benzodiazepinas. Cognitivo. Metadona. Dolor.* Screening.

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## INTRODUCTION

The use of opioid analgesics in acute, chronic cancer and non-cancer pain increases every year[1], due to a higher incidence of these painful conditions (i.e., post-herpetic neuralgia, diabetic neuropathy, and rheumatologic diseases). Prescriptions of methadone showed the greatest percentage increase in sales from 1997 to 2007; however, clinical outcomes are often unsatisfactory due to limited analgesic efficacy or the incidence of side effects including central nervous system involvement[2]. Opioid use affects brain function, but the consequences of chronic use in the human brain are unclear. In cultured neuroblastoma cells, high concentrations of methadone induce cell death by necrosis, primarily by a decrease in adenosine triphosphate levels and secondarily by a marked increase in the permeability of the mitochondrial membrane[3]. With opioid exposures of months to years, cerebral evaluation using functional magnetic resonance imaging (fMRI) showed a decrease in the functional connectivity and cell volume of the amygdala compared to healthy controls. These changes were related to the duration of exposure[4]. Another fMRI study found that patients receiving methadone had disruptions in a cerebral-cerebellar circuit closely related to working memory and a countervailing increase in neural activity within that circuit in patients[5].

Cognitive impairment may be chronic and progressive (dementia) or mild (no dementia); although both entities are defined in the literature, in clinical practice, the distinction between particular conditions of mild cognitive disorders sometimes requires complex neuropsychological tests that are not always available. Symptoms of mild cognitive disorders are vague and may include memory loss, language disturbance, attention deficit, and disorientation[6,7]. Patients on opioid therapy may experience significant impairment in different cognitive domains such as working memory and cognitive flexibility[8]. The strategies being used to identify or reduce opioid-related cognitive effect include appraising and monitoring of cognitive status, using lower doses in geriatric patients, and minimizing concomitant use of other psychotropic medications[9].

Long-term cognitive disorders associated with opioid use in cancer pain patients was found in up to 77% of advanced cases[10]; a review of controlled studies found an association between poor cognitive performance and opioid use[11]. However, in a systematic review of 13 trials (three of them randomized, blind, and controlled), no cognitive disorders were found with the use of opioids[12]. In addiction treatment, the results are different. While dependent patients treated with buprenorphine performed better on memory tests in comparison to patients receiving methadone, they showed greater cognitive deficits in working and verbal memory[13]. Thus, the cognitive effects of opioids remain an open topic in relation to the therapeutic use of these drugs.

In light of the increasing use of methadone, the present study was undertaken to: characterize the pattern of use of methadone at a university hospital; describe the characteristics of patients who received it; and test for characteristics associated with cognitive disorders among patients receiving methadone.

## MATERIALS AND METHODS

This retrospective study explored the use of methadone during a defined period.

### Study setting

The study was performed at a 200-bed teaching hospital that provides care in most medical and surgical specialties, including acute post-operative pain, chronic non-cancer pain, and palliative medicine. Recently, an institutional policy encouraged adequate pain treatment, according to the hospital quality standards set by the U.S. International Joint Commission. The requirements of the Ministry of Health state that to fill methadone prescriptions, the doctor must hold a current professional license and indicate the plan of use of this drug. There are no other significant administrative or economic constraints for hospital use because methadone is included in the National Mandatory Health Plan (i.e., meaning that the state provides it without direct cost to the user). The protocol was submitted and approved by the Institutional Review Board.

### Inclusion and exclusion criteria

To identify the patients, the electronic database of the Hospital Pharmacy Service was screened to identify all methadone prescriptions for patients hospitalized from January 1, 2012, to May 31, 2013. All patients who had not received methadone during the study period were excluded, as were patients with dementia.

### Data collection

The medical records of all eligible patients were reviewed. To ensure accuracy, information was collected by a nurse with experience in auditing medical records.

When doubts regarding clinical information arose, the records were reviewed by a second researcher and doubts were resolved by consensus. Retrieved variables included drug utilization characteristics, analgesic response, and side effects. All data related to methadone use and pain treatment refer to the in-hospital period during which the patient received analgesic treatment. An initial pain score (0 to 10) was documented immediately before methadone treatment and final intensity score on the last day recorded during methadone treatment.

### Study variables

The complete list of variables included:

- Demographic information, clinical data, pain score (0 = no pain, 10 = worst possible pain), and comorbidities;
- Presence of cognitive disorders (delirium, significant impairment of memory recognized by a family member or caregiver, an impaired-level Folstein mental questionnaire score lower than 24/30, or a formal diagnosis made by a psychologist or psychiatrist of any type of cognitive disorder);
- Information related to the methadone prescription: prescriber, initial and final dose (mg), dosing intervals, days of treatment, and side effects;
- Additional treatments: data regarding the use of nonsteroidal anti-inflammatory drugs, benzodiazepines, antidepressants, anticonvulsants, and corticosteroids.

### Statistical analysis

Stata 10.0 software was used for the statistical analysis. Initially, an exploratory analysis was performed and was followed by a descriptive analysis in which frequency tables were constructed. The variables age, gender, diagnostic categories, anatomic site of pain, complaint, type of pain, and nature of pain were presented as frequency distributions. Categorical variables were summarized with frequencies and percentages. The Shapiro-Wilk test was used to validate the normal distribution of data for continuous variables and when normality was found, the mean and standard deviation (SD) were reported. Otherwise, the median and interquartile ranges (IR) were reported. To determine differences in the intensity of pain, the paired Student's *t*-test was used because of the finding that the difference (before vs. after treatment) showed a normal distribution.

In bivariate analysis, the association of demographic and clinical variables with cognitive disorder was evaluated using the asymptotic association test, the chi-square test without correction, and with Yates corrections, the truth reasoning test with exact proof, the exact Fisher test, and the reasoning of likelihood (expected values < 5). The strength of the association was assessed using the relative risk (RR) and the respective 95% confidence intervals (CI). For quantitative variables that met the normality assumption, the Student's *t*-test was used for independent groups with homogeneous and heterogeneous variances.

The set of explanatory variables (initial and final dose, age, gender, antidepressant/anticonvulsant, type of pain), and variable for cognitive disorders were obtained by conditional logistic regression with hierarchical model selection; due to the retrospective cohort design, the odds ratio (OR) was used as an estimate of the relative risk. The goodness of fit of the model was measured with the Hosmer-Lemeshow test and the likelihood test. The statistical tests were evaluated at a significance level of 5% ($p < 0.05$).

## RESULTS

This retrospective study (17 months) included 73 patients (38 women; 52.0%) who received methadone and met the inclusion criteria; all came from urban areas. Patients younger than 30 years accounted for 21.9% of the study sample (n = 16); 34.2% (n = 25) were patients aged 31-60 years, 23.2% (n = 16) were aged 61 to 74 years, and those older than 74 years accounted for the remaining 20.5% (n = 15).

According to the most relevant clinical condition, patients were grouped into 10 diagnostic categories (Table 1); more than three quarters of the study sample (79.4%; n = 58) had chronic conditions.

For most patients, pain was the hospital admission diagnosis (64.4%; n = 47); other reasons included general deterioration (8.2%; n = 6), respiratory distress (6.9%; n = 5), surgery (5.5%; n = 4), fever and withdrawal (4.1% each; n = 3), cognitive disorders (2.7%; n = 2), and monitoring, edema, and unknown reason (1.4% each; n = 1).

Methadone was mostly prescribed by doctors of the Pain and Palliative Care Clinic (75.3% of the study sample; n = 55); other prescribing doctors belonged to medical subspecialties (19.2%; n = 14), surgical subspecialties (2.7%; n = 2), and onco-hematology and psychiatry (1.4% each; n = 1).

**Table 1. Diagnosis of the 73 patients studied**

| Diagnostic category | (n) | % |
|---|---|---|
| Chronic pain | | |
| – Neoplastic disease | 36 | 49.3 |
| – Vascular disease | 6 | 8.2 |
| – Skeletal muscle disease | 6 | 8.2 |
| – Neurological disease | 4 | 5.5 |
| – Immunological disease | 3 | 4.1 |
| – Metabolic disease | 2 | 2.7 |
| – Infectious disease | 1 | 1.4 |
| TOTAL Chronic pain | 58 | 79.4 |
| Other | | |
| – Acute pain | 7 | 9.6 |
| – Abstinence maintenance | 7 | 9.6 |
| – Related to pregnancy | 1 | 1.4 |
| TOTAL Other | 15 | 20.6 |

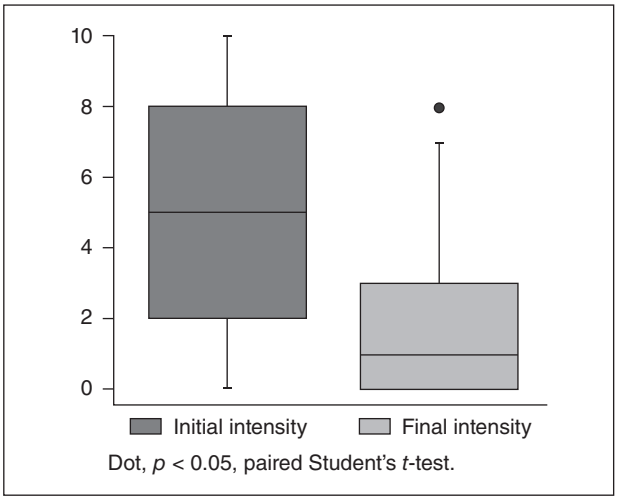


**Figure 1.** Variation in the intensity of pain (0-10) from the first day to the last day of treatment.

## Use of methadone and characteristics of pain

The most common methadone indication was "pain" (90.4% of patients; n = 66) and the average duration of analgesic treatment was 9.9 days (SD: 11.9). Almost half of the patients treated with methadone had somatic pain (47.9%; n = 35); this was followed by mixed (31.5%; n = 23), neuropathic (10.6%; n = 8), and visceral pain (9.5%; n = 7).

The mean initial pain intensity was 4.8/10 (SD: 3.3) and the mean final intensity was 1.8/10 (SD: 2.0). Patients with neuropathic pain had a higher mean initial pain intensity (6.1/10; SD: 2.6), which reached a mean score of 3.1/10 (SD: 1.6) by the end of treatment.

Almost half of the patients received methadone for cancer pain (49.3%; n = 36); in these patients, the mean initial pain intensity was 5.8/10 (SD: 3.3) and the mean final pain intensity was 1.9/10 (SD: 2.1). Other patients used methadone for chronic pain (31.5%; n = 23); their mean initial and final pain intensities were 4.6/10 (SD: 3.0) and 2.2/10 (SD: 1.9), respectively. Seven patients (9.5% of the study sample) were treated for severe pain; their mean initial and final pain intensities were 4.7/10 (SD: 2.9) and 0.5/10 (SD: 1.1), respectively. The last group of seven patients (9.5%) received methadone for withdrawal prevention; among these patients, the mean initial pain intensity score was 1.4/10 (SD: 2.9). Figure 1 shows the initial and final pain intensities.

Two variables were significantly associated with final pain intensity: the nature of the pain (chronic [p = 0.003] vs. cancer pain [p = 0.007]), and the initial pain intensity (p = 0.007) (Table 2).

Regarding the doses of methadone, the mean initial dose was 24.7 mg (SD: 24.1) and the mean final dose was 23.5 mg (SD: 25.4).

## Concomitant treatments and adverse drug reactions

In addition to methadone, half of the patients received acetaminophen (50.6%; n = 37), 46.5% received antidepressants/anticonvulsants as co-analgesics (n = 34), and 32.8% (n = 24) received benzodiazepines (Table 3). No significant differences in pain intensity were found at the end of treatment among those who received and did not receive these medications. For purposes of opioid "rescue" for incidental pain, prescribers mainly used hydromorphone hydrochloride (56.2%; n = 41).

The comorbidities most frequently associated with methadone treatment were hypertension (38.3%; n = 28), constipation (36.4%; n = 27), nausea and vomiting (26%; n = 19), diabetes (17.8%; n = 13), and depression (12.3%; n = 9). No significant differences were found

**Table 2. Independent variables associated with the final intensity of pain**

| Variable | Final pain range mean (IR) | p value* |
|---|---|---|
| Nature of pain | | |
| – Chronic | 2.5 (0-4) | 0.003 |
| – Cancer-related | 2 (0-4) | 0.007 |
| Initial pain intensity | | 0.007 |

*Negative binomial regression. IR: interquartile range.

**Table 3. Drugs administered concomitantly with methadone treatment**

| Drug | (n) | % |
|---|---|---|
| Opioids | | |
| – Hydromorphone | 41 | 56.2 |
| – None | 17 | 23.3 |
| – Morphine | 9 | 12.3 |
| – Fentanyl | 5 | 6.9 |
| – Other | 1 | 1.4 |
| Benzodiazepines | | |
| – None | 49 | 67.1 |
| – Others | 9 | 12.3 |
| – Alprazolam | 6 | 8.2 |
| – Lorazepam | 6 | 8.2 |
| – Zolpidem | 3 | 4.1 |
| Antidepressants/anticonvulsants | | |
| – None | 39 | 53.4 |
| – Gabapentin | 9 | 12.3 |
| – Pregabalin | 9 | 12.3 |
| – Other | 8 | 11.0 |
| – Quetiapine | 5 | 6.9 |
| – Sertraline | 2 | 2.7 |
| – Duloxetine | 1 | 1.4 |
| Corticosteroids | | |
| – Yes | 21 | 28.8 |
| – No | 52 | 71.2 |

between the doses received by patients who presented and who did not present these events or conditions.

## Cognitive disorders

The clinical characteristics of the 19 patients who presented cognitive disorders were analyzed. No significant differences were observed in the mean age (59.1 [SD: 22.7] vs. 50.8 [SD: 20.6]) or sex between those who did and did not have cognitive disorders. There was no significant dependence of the incidence of cognitive disorders on the different types of pain or on the initial/final pain intensities. Additionally, the presence of cognitive disorders was not significantly associated with the type of pain ($p = 0.271$; exact likelihood ratio test), nor with the initial (27.6 vs. 23.7; $p = 0.439$) or final methadone doses (29.6 vs. 21.3; $p = 0.387$) (Mann-Whitney exact test, one-tailed).

In the present sample, chronic and neuropathic pain were strongly associated variables (Fisher exact test: $p = 0.003831$), but neither was associated with cognitive disorders. Patients on methadone who developed cognitive disorders presented diverse comorbidities: hypertension, renal disease (36.8%; n = 7), hypothyroidism or peripheral vascular disease (31.5%; n = 6 each), chronic pulmonary disease (26.3%; n = 5), and depression (21%; n = 4).

Almost one-third of the study sample (32.8%; n = 24) received methadone and benzodiazepines concomitantly and 10 of these patients (41.7%) had cognitive disorders (Table 4). This proportion was significantly higher than in those who had not received benzodiazepines (18.4%; $p = 0.034$; Fisher's exact test, one-tailed; RR: 2.26 [95% CI: 1.064-4.834]). No significant differences in cognitive disorders were found among methadone-treated patients concomitantly receiving antidepressants (52%; n = 10), corticosteroids (21%; n = 4), anti-inflammatory drugs, acetaminophen, or other opioids.

## Multivariable analysis

The regression model (Table 5) showed that the final dose of methadone was significantly related to cognitive disorders factors (the higher the dose, the greater the probability of impairment), as was age greater than 60 years (OR: 7.85; 95% CI: 1.54-40.04), benzodiazepine use (OR: 6.48; 95% CI: 1.42-29.65), and being male (OR: 5.60; 95% CI: 1.36-22.99).

**Table 4. Benzodiazepine use and cognitive impairment**

| | | Cognitive impairment | | |
|---|---|---|---|---|
| | | Yes | No | Total |
| Yes | n | 10 | 14 | 24 |
| | % Within benzodiazepines + | 41.7% | 58.3% | 100.0% |
| | % Within cognitive impairment category | 52.6% | 25.9% | 32.9% |
| No | n | 9 | 40 | 49 |
| | % Within benzodiazepines - | 18.4% | 81.6% | 100.0% |
| | % Within cognitive impairment category | 47.4% | 74.1% | 67.1% |
| Total | n | 19 | 54 | 73 |
| | % of study population | 26.0% | 74.0% | 100.0% |

**Table 5. Logistic regression model for cognitive impairment**

| Explanatory variable | B* | E.T.† | p value | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Final dose | 0.036 | 0.016 | 0.019 | 1.04 | 1.006 | 1.069 |
| Age ≥ 60 | 2.060 | 0.832 | 0.013 | 7.85 | 1.538 | 40.036 |
| Benzodiazepine + | 1.869 | 0.776 | 0.016 | 6.48 | 1.418 | 29.649 |
| Male | 1.723 | 0.721 | 0.017 | 5.60 | 1.364 | 22.992 |
| Chronic | –4.825 | 1.297 | 0.000 | 0.008 | | |

*B.
†E.T.: regression coefficients.
OR: odds ratio; CI: confidence interval.

## DISCUSSION

The main finding of this retrospective observational study was that a quarter of patients with no obvious cognitive disorders before treatment developed it during methadone treatment. Although this type of study does not establish a causal link, it confirms the need for systematic monitoring for cognitive disorders; higher risk of cognitive disorders could be seen in men, in patients aged 60 years and older, those exposed to benzodiazepines, and those on a higher methadone dose. This result is in agreement with earlier reports that showed the prevalence of cognitive disorders in patients receiving opioid agonists to be one out of three patients[14], those at higher risk being the elderly and those requiring high doses.

The results of this study reflect usual clinical practice and the results could be relevant to health professionals working in similar settings in general university hospitals. First, cognitive disorders screening involves recording findings at baseline, before treatment, by the end of methadone treatment, and probably at intermediate stages depending on clinical needs such as a dose increase or when starting other medicines. The screening may include a questionnaire such as the Folstein Mini Mental with the proper adjustments for age and education, semi-structured interviews for caregivers, or a diagnostic process by a psychologist or psychiatrist. The situation is relevant because some factors associated with cognitive disorders may be modified by the prescriber. This modification could be done by reducing benzodiazepine use, by promoting non-pharmacological therapies, and by using strategies to reduce exposure to methadone such as regional anesthesia techniques or optimizing the use of non-opioid medicines.

Cognitive disorders: identifying associated factors to reduce impact. Other important factors should be taken into account as the presence of pain is associated with decreased working memory and executive functions[15]. The optimum outcome would be adequate pain control while maintaining a minimal use of opioids. In this study, this balance was achieved in a little more than half of the patients.

The findings of this study potentially underestimate the true dimensions of the problem because the number of patients found to be adversely affected by opioids could have been greater if a specialized neuropsychological assessment had been done as a matter of routine. This lack of screening, common in general hospitals, limits the ability to determine whether cognitive disorders existed prior to the use of methadone and was aggravated by its use, or if it started with methadone use.

The use of benzodiazepines has repeatedly been implicated as responsible for cognitive disorders. In our sample, about half of the patients received a benzodiazepine and its use was significantly associated with cognitive disorders. Notably, a study in a Latin American general hospital[16] found that the prevalence of psychiatric medication was only 38.7%, indicating the need to reevaluate the use of these drugs in our population. In addition, there is a potential opioid interaction with alprazolam and other benzodiazepines due to a common metabolic pathway, through CYP450, that can synergistically increase toxicity to the central nervous system.

The prescribing clinician may decide to favor or not favor preservation of brain functions, highlighting the role of an individualized prescription. This study contributes to the current research on the use of methadone in chronic non-malignant pain patients, as recent data showed that the increase in the use of methadone is accompanied by a rise in unintended overdose deaths[17].

An important recommendation is the participation of a family member to inform the health team about cognitive changes of the patient.

## Relieving pain

Pain relief is a patient-centered outcome. A number of patients (64.4%) admitted to the hospital for treatment of uncontrolled pain were discharged without achieving this therapeutic goal; although the data does not fully reveal the circumstances of intake, it can be assumed that some patients might have received more-effective treatment. Optimization would include use of non-opioid analgesics, early treatment of side effects, and education of personnel in non-pharmacological treatments.

As this study was conducted in a general hospital, methadone was used relatively frequently because of its effectiveness in the treatment of pain. This finding is consistent with most research that defines an increasing role for methadone in pain from cancer either as an initial treatment or as an alternative in patients with opioid tolerance or toxicity[18,19]. Also notable is its use in this setting to prevent withdrawal symptoms in patients exposed for prolonged periods to opioids in intensive care units, which are then suspended sharply; in those patients, preventing withdrawal syndrome helps to restore homeostasis.

Only a minority of patients was treated with methadone for acute pain. This low utilization is consistent with most guidelines for the management of acute pain that assign a secondary role to methadone versus morphine or fentanyl. One of the main arguments for relegating methadone to a secondary role in acute pain is its long elimination half-life, which complicates adaptation to rapidly changing situations in acute settings.

Among all patients starting treatment with methadone, the median pain intensity was 5 (IR: 2-8) and was reduced to 1 (IR: 0-3) by end of treatment. Although this reduction was statistically significant ($p < 0.001$), symptomatic relief was not achieved in nearly a quarter of patients (23.3%), as evidenced by higher-than-average final pain intensities (4/10). Several explanations may help to understand these results. First, the limited number of patients receiving co-analgesics (52.0%; n = 38) was contrary to the current recommendations to combine drugs with different mechanisms of action for optimal analgesic effect. In addition, some of our subjects had neuropathic pain. In our patients with neuropathic pain, who scored lower for analgesic response to methadone treatment with higher intensities of pain at the end of treatment (3.1/10) compared with other types of pain, relatively adequate results were nonetheless achieved. This finding is consistent with previous reports that indicate a lower clinical response to opioid analgesics in this type of pain[20]. Racemic methadone also has a non-opioid mechanism of action, N-methyl-D-aspartate (NMDA) receptor blockade, and may have greater analgesic efficacy than other opioid analgesics[21]. Moreover, opioids used in "rescue" mode do not influence cognitive disorders.

A finding of an initial pain score of 5.8/10 in patients with cancer pain deserves special consideration. In this group of patients with uncontrolled pain, methadone has an essential role as an alternative medication to overcome any lack of analgesic efficacy due to pharmacological tolerance. The efficacy of methadone was also reflected in chronic pain patients who, at the end of therapy, had an intensity of 2.2/10, reflecting adequate pain control.

A significant finding of this study is the relationship between greater pain intensity at the end of treatment and (i) greater pain intensity at the beginning of analgesic treatment, (ii) the presence of cancer pain, and (iii) chronic pain. Only the first condition is modifiable through effective management of analgesics. In the other two conditions, the higher initial intensities of pain may be the result of greater tissue damage induced by cancer and the chronic nature of the pain that creates abnormal neural circuits that perpetuate pain[22]. These factors could be related to the higher pain intensity findings reported in a comparable previous study[23].

This research showed that methadone is a medication prescribed primarily by specialists in the Pain and Palliative service; i.e. doctors familiar with the use of methadone and who follow the recommendations of experts[24]. This selective prescribing could contribute to non life-threatening adverse events such as ventricular arrhythmias with doses above 100 mg daily[25].

Clinical uses were as widely varied as the doses used, consistent with the characteristic variability in analgesic requirements routinely observed in clinical practice. Patients receiving methadone for prevention of relapse to substance abuse (i.e., for abstinence) had lower pain intensity scores that varied minimally over the course of treatment; is noteworthy that this was the only group of patients in whom the use of methadone decreased, from 25.7 to 17.5 mg/day. The doses used to prevent withdrawal symptoms matched those recommended, varying between 5 and 40 mg/day.

For most patients (54.7%; n = 40), monitoring of methadone treatment was short-term (6 days or less). This follow-up may be brief for geriatric patients who show a longer elimination half-life and therefore require more time to show fully the effects of methadone. It is estimated that due to the long half-life of methadone, it would take weeks to achieve a steady state.

The presence of nausea and vomiting, which occurred in a quarter of our sample, is an important

symptom that impairs wellness and can lead to electrolyte imbalances. In the study sample, there was no significant clinical difference in methadone dose among patients who experienced nausea and vomiting. At the same time, constipation, which occurred in one of three patients, should also be prevented, as it can be a source of concern for the patient.

### Limitations

This study has several limitations. First, its retrospective nature can create information bias. This limitation could be minimized using electronic hospital records of different origin that are more accurate in some ways, providing corroboration of information obtained from a clinical database by other administrative information. The small size of the sample limits the interpretation of results and the achievement of statistical significance; but our findings represent routine use over an extended period and have great value to clinicians with similar practices.

## CONCLUSION

Methadone possesses a suite of properties suitable for treating persistent pain; however, proper methadone use requires skilled monitoring to avoid poor pain control and negative effects on cognitive function. It is necessary to periodically review the new published evidences of in-hospital use of methadone in order to provide appropriate feedback to the healthcare team. The evaluations of baseline and end-of-treatment cognitive status should be part of a proper prescription, for early recognition and to decrease the negative impact of cognitive disorders on the quality of life and providing the ability to modify treatment rationally. The results showed the importance of an optimal use of non-opioid analgesics, and limiting the use of benzodiazepines. These recommendations should be included in clinical practice guidelines because providing uniform care may lead to better clinical outcomes.

## DISCLOSURE OF INTEREST

The authors declared no conflict of interest.

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