

# First-Line Methadone For Cancer Pain. Titration Time Analysis

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# Abstract

**Background.** Methadone is a low-cost, strong opioid that is increasingly used as a first-line treatment for pain in palliative care (PC). Its long and unpredictable half-life and slow elimination phase can make titration challenging. Evidence for titration modalities is scarce.

**Objective.** To describe the titration phase of the treatment with low dose first-line methadone and the use of methadone for breakthrough pain.

**Methods.** Prospective study with strong opioid-naïve patients with moderate to severe cancer pain followed at a tertiary PC unit in Argentina. Starting methadone dose was 2.5-5 mg/day every 8, 12, or 24 hours. Titration allowed daily dose increases from Day 1, and prescription of oral methadone 2.5 mg every 2 hours with a maximum of 3 rescue doses/day for breakthrough pain. Pain control, methadone stabilization dose, and adverse effects, among other variables, were daily assessed over the first 7 days (T0 – T7).

**Results.** 62 patients were included. Initial median (IQR) methadone dose was 5(2.5) mg/day. Pain intensity decreased from a median (IQR) of 8(2.3) at T0 to 4(2.3) at T1 and remained  $\leq 4$  until T7 (all  $p < 0.0001$  compared to T0). Similar results were obtained through the categorical and tolerability scales for pain. Fifty patients (81%) reached pain control, 66% in the first 48 hours. Methadone daily dose at T2 and T7 were higher than that at T0: 7.5(3) and 6.7(5.5) versus 5(2.5); respectively (all  $p < 0.05$ ). The opioid escalation index at T7 was 1.7%. The median (IQR) number of rescues, stabilization dose and time for stabilization were 0 (1), 5(4.5) mg and 3(2) days, respectively. Two patients were discontinued due to delirium. All the other side effects were mild.

**Conclusions.** First-line, low-dose methadone using rescue methadone resulted in a pronounced and rapid decrease in pain, with minimal need for titration and for breakthrough doses, and no evidence of accumulation or sedation by the end of the week.

## Introduction

Moderate to severe pain affects 70–90% patients with advanced cancer and requires strong opioids as main treatment [1]. Methadone is a synthetic strong opioid with several distinctive advantages in comparison to morphine and other extended-release opioids. It has a fast-initial absorption-distribution phase with a rapid onset of analgesic effect, a long half-life that allows convenient administration intervals of 8 or 12 hours and a low rate of induction of tolerance and hyperalgesia [2–5]. Of special interest is its low cost, given the existence of significant barriers to access to opioids in low- and middle-income countries (LMIC) [6]. However, methadone has complex pharmacological properties that has traditionally limited its use to specialized teams and mainly as a second or third line of treatment. A main concern relates to its variable and erratic half-life and slow elimination phase with the risk of accumulation and delayed toxicity [5, 7], requiring cautious initiation and titration. In recent years, some studies began to document methadone's safety and efficacy as a first line of treatment for cancer pain in palliative care (PC) patients [8, 9]. Still there is limited evidence in relation to the modality of titration and the timing for pain control and dose stabilization [8]. Based on methadone's pharmacokinetics, it is expected that most patients achieve dose stabilization within the first week of treatment [5]. Our aim was to describe this critical period of dose titration in patients treated with first line methadone for the management of cancer pain.

## Methods

## **Study design and patient eligibility**

Prospective single-center, observational study of first-line methadone titration during the first seven days of treatment for the management of cancer pain. All patients gave their informed consent to participate. This study was reviewed and approved by the Institutional Review Board and was granted by the National Cancer Institute, Argentina. All adult strong opioid-naïve ambulatory or inpatients who consulted to the PC unit (PCU) between 12/1/2016 and 9/30/2018 and initiated methadone for the treatment of moderate to severe cancer pain according to the categorical pain scale (see below) were included. Patients had normal cognition defined by the Memorial Delirium Assessment Scale (MDAS) [10] and life expectancy  $\geq 4$  weeks according to clinical judgment. Those patients with contraindications to taking oral methadone, not able to understand the indications or in high risk for methadone misuse, were not eligible.

### **Methadone titration**

At T0, patients were started on oral methadone 2.5-5 mg/day every 8, 12, or 24 hours. Elderly or frail patients (> 70 years old or with cancer cachexia with major weight loss) were started with the lower doses (2.5-5 mg/day), while on the other hand younger patients with poor prognosis pain syndrome (neuropathic component, incidental pain) were started with the higher ones (10–15 mg/day). The titration regime allowed daily dose increases from day 1 with the prescription of rescue oral methadone 2.5 mg every 2 hours with a maximum of 3 rescue doses/day. This titration strategy is faster than usual, with a delay of 5–7 days for dose increases [5], and it relies on the possibility of daily close monitoring of the patients at the PCU. Adjustment in adjuvant analgesics as part of routine opioid pain management was conducted by the clinician. All patients were receiving stable dose of other drugs by the time methadone was introduced. Methadone was discontinued due to the occurrence of a) limiting adverse effects, b) loss of oral route, c) cognitive impairment, d) patient lost to follow, or e) patient decision to discontinue the study.

### **Variable assessment**

Patients were monitored daily through face-to-face or telephone consultation for the first 7 days (T1-T7), which is the usual and acceptable time to titrate methadone dose against pain [5, 11]. Follow-ups over the phone were always conducted directly with the patient. Main outcomes were achievement of control pain and stable methadone dose, number of rescue doses and presence of adverse effects (AE).

The pain syndrome was evaluated both clinically and by using the Edmonton Staging System (ESS) classification for pain [12]. Patients were asked to indicate the intensity of pain in the last 24 hours through the numerical (from 0 to 10) and the categorical (no, mild, moderate, or severe pain) [13] scales. A face validated tolerability scale was also used to establish how tolerable the pain had been in the last 24 hours (fully, moderately, little, or non-tolerable pain). Controlled pain was considered when there was an improvement  $\geq 30\%$  or  $\geq 2$  points in the numerical pain score [14, 15], together with having mild to no pain in the categorical scale and moderately to fully tolerable pain in the tolerability scale, for at least 48 hours, in the absence of limiting AE. Additionally, patients were asked for their personalized pain goal (PPG) by identifying the maximal intensity of pain they would still consider comfortable [16].

The methadone daily dose was considered that prescribed plus rescues in the last 24 hours. The stabilization dose was considered that in which the patient could remain without requiring adjustment or requiring a variance in dose  $\leq 20$  without limiting AE. Time to reach a stable daily dose was considered as the number of days

between first dose and first day on stable dose [17]. The opioid escalation index as a percentage (OEI%) was calculated as  $[(MFD-MID)/MID]/days \times 100$ , where MFD and MID are methadone final and initial (indicated at T0) doses [11].

The presence of delirium (considered as  $\geq 7$  in MDAS) [18], hallucinations, myoclonus, constipation (considered as  $\geq 3$  days without bowel movements), other symptoms intensity evaluated through the Edmonton Symptom Assessment System (ESAS) [19], the Eastern Cooperative Oncology Group (ECOG) performance status [20], and the need for adjuvant medication, were also determined.

### **Statistics**

Demographics and baseline characteristics were summarized by descriptive statistics using median and range or median and interquartile range (IQR) for continuous variables and frequency and proportions for categorical variables. Medians were compared through the Mann Whitney and Wilcoxon signed rank tests. Percentages were compared through the  $\chi^2$  and Fisher exact test. Significance levels  $< 0.05$  were considered statistically significant. An intention-to-treat (ITT) analysis was performed, where all participants who met the inclusion criteria but did not complete the 7-day study period were considered as non-responders to pain control and included in the statistical analysis.

## **Results**

### **Patient characteristics and baseline assessments**

Sixty-two patients were included. Patient accrual is shown in Fig. 1. Prescribed median (range) methadone daily dose was 5.0 (2.5–10) mg with rescues of 2.5 mg with a maximum of 3 rescue doses a day. None of the patients required more than 3 rescues. Patient demographics and medical characteristics at baseline (T0) are shown in Table 1. Most were outpatients, with advanced cancer, predictors of poor response to opioids (ESS = 2), pain score  $\geq 4$ , and little tolerable to intolerable pain. Initial median (range) pain intensity was 8 (4–10) and the PPG was 2 (0–4). Irruptive pain was present in 11/62 patients (18%) with a median intensity of 7 (6–9).

Table 1  
Patient demographics and baseline medical characteristics

<b>N = 62</b>	<b>N</b>	<b>%</b>
Median age (range)	61 (32–85)	
Men	32	52%
Frail/elderly	3	5%
Outpatients	54	87%
1st consultation to the PCU	44	71%
Previous history of drug addiction	8	13%
CAGE (+) <sup>a</sup>	9	15%
TUMOR SITE:		
Gastrointestinal	16	26%
Lung	14	23%
Breast	9	15%
Prostate	6	10%
Other/Unknown	17	26%
TUMOR STAGE:		
Advanced	56	90%
Localized	1	2%
Unknown/Under study	5	8%
TREATMENT:		
Active	27	44%
Under study	27	44%
Inviabile/Discontinued	8	13%
PREVIOUS ANALGESIA:		
No opioids (acetaminophen/NSAIDS)	35	56%
Mild opioids (tramadol-codeine)	27	44%
TYPE OF PAIN:		
Nociceptive	41	66%

<sup>a</sup>: CAGE (cut-annoyed-guilty- eye) questionnaire (+): Was considered with 2 positive responses for men and 1 for women. Abbreviations: <sup>b</sup> Edmonton Symptom Assessment System. <sup>c</sup> Edmonton Staging System. <sup>d</sup> Eastern Cooperative Oncology Group scale for performance status. <sup>e</sup> IQR: interquartile range

<b>N = 62</b>	<b>N</b>	<b>%</b>
Mixed	19	31%
Neuropathic	2	3%
<b>PAIN INTENSITY:</b>		
ESAS <sup>b</sup> score $\geq$ 4	61	98%
Moderate to severe pain	62	100%
Little tolerable to intolerable pain	52	84%
ESS <sup>c</sup> = 2	37	60%
ECOG <sup>d</sup> = 3 or 4	25	40%
ESAS <sup>b</sup> score	Median (IQR <sup>e</sup> )	
Pain	8 (2)	
Nausea	0 (0)	
Drowsiness	3 (5)	
Asthenia	7 (2.2)	
Anxiety	4 (6)	
Depression	3 (5)	
Appetite	5 (8)	
Dyspnea	0 (2.3)	
Insomnia	3.5 (8)	
Wellbeing	5 (4)	
<sup>a</sup> : CAGE (cut-annoyed-guilty- eye) questionnaire (+): Was considered with 2 positive responses for men and 1 for women. Abbreviations: <sup>b</sup> Edmonton Symptom Assessment System. <sup>c</sup> Edmonton Staging System. <sup>d</sup> Eastern Cooperative Oncology Group scale for performance status. <sup>e</sup> IQR: interquartile range		

## Follow up

Fifty-five out of 62 patients who initiated methadone (89%) completed the 7-day observation period. Among the 7 patients who discontinued (11%), 2 were withdrawn due to delirium on day 5 (one of them possibly related to hypercalcemia), 1 due to loss of oral route on day 4, and 4 abandoned the protocol at their own decision on days 1, 1, 3 and 5. In the latter, reasons included frailty to answer questions, non-confidence to methadone or non-adherence.

According to the ITT analysis where those patients who discontinued the study were considered to have failed, pain control was achieved in 50/62 patients (81%), 33 of them (53%) at T1, 8 (13%) at T2, 3 (5%) at T3, 5 (8%) at

T4 and 1 (2%) at T5. Of the patients who completed the study, 5 (8%) did not reach controlled pain. Three of them remained with mild or no pain and quite to fully tolerable pain along the whole week, although without reaching the criteria for controlled pain. The remaining 2 had not achieved pain control by Day 7. Subsequent follow-up of these 2 patients showed that one of them achieved a pain ESAS score = 2 at day 14 while the other was still in high pain by day 28 (data not shown).

From T1, there was a significant decrease in patients reporting pain intensity  $\geq 4$ , moderate to severe pain or little tolerable to intolerable pain (Table 2). Median (IQR) ESAS score for pain decreased from 8 (2) at T0 to 4 (2.3) at T1, 3 (2.5) at T3 and 2 (4.5) at T7 (all  $p < 0.0001$  compared to T0) (Fig. 2A). Twenty-two patients (35%) reached their PPG; another 14 (23%) achieved a pain score equal to their expressed PPG plus one point.

Table 2

Presence of symptoms that could be potentially affected by methadone at days 0, 1, 3 and 7 on methadone. Pain was assessed through the numerical, categorical and tolerability scales, and analyzed through the intention-to-treat analysis

	T0	T1	T3	T7	T1vsT0	T3vsT0	T7vsT0
	Number (%) of patients				P (Fisher Exact test)		
Pain intensity $\geq 4$	61/62(98%)	28/62(45%)	18/62(29%)	25/62(40%)	$< 0.0001$	$< 0.0001$	$< 0.0001$
Moderate to severe pain	62/62(100%)	12/62(19%)	13/62(21%)	14/62(23%)	$< 0.0001$	$< 0.0001$	$< 0.0001$
Little tolerable to intolerable pain	52/62(84%)	10/62(16%)	9/62(15%)	8/62(13%)	$0.0001$	$< 0.0001$	$0.0001$
Severe (ESAS <sup>a</sup> $\geq 7$ ) nausea	6/62(10%)	4/60(7%)	1/59(2%)	5/55(9%)	NS	NS	NS
Severe (ESAS <sup>a</sup> $\geq 7$ ) drowsiness	5/62(8%)	4/60(7%)	5/59(8%)	10/55(18%)	NS	NS	$0.0042$
Severe (ESAS <sup>a</sup> $\geq 7$ ) dyspnea	0/62(0%)	2/60(3%)	0/59(0%)	1/55(2%)	-	-	-
Constipation	-	-	3/59(5%)	4/55(7%)	-	-	-
Delirium	0/62(0%)	0/60(0%)	0/59(0%)	2/55(4%)	-	-	-
Hallucination	0/62(0%)	3/60(5%)	4/59(7%)	3/55(5%)	-	-	-
Myoclonus	0/62(0%)	3/60(5%)	8/59(14%)	5/55(9%)	-	-	-

<sup>a</sup> Edmonton Symptom Assessment System score

Variations in the proportion of patients with symptoms and side effects attributable to methadone are shown in Table 2. The presence of severe (ESAS score  $\geq 7$ ) nausea and dyspnea did not rise from T0, while severe drowsiness significantly increased at T7. Constipation, as considered  $\geq 3$  days without bowel movement, was present in 3 patients at T3 and 4 at T7. Two patients had delirium at T7 determining rotation to morphine. Hallucinations and myoclonus were all isolated and not clinically relevant. No coma events nor respiratory depression occurred. ESAS scores for symptoms are shown in Table 3. Nausea and drowsiness remained low throughout the study period, while dyspnea, wellbeing, asthenia, depression, anxiety, insomnia, and appetite significantly decreased from T1 or T3.

Table 3  
Edmonton Symptom Assessment System score for symptoms in the precedent 24 hours, assessed at days 0, 1, 3 and 7 on methadone

	T0	T1	T3	T7	T1vsT0	T3vsT0	T7vsT0
	Median (IQR <sup>a</sup> )				P (Wilcoxon test)		
Nausea	0 (0)	0 (3)	0 (0)	0 (0)	0.9714	0.1079	0.4795
Drowsiness	3 (5)	1 (5)	0 (4)	0 (5)	0.2358	0.0849	0.3652
Dyspnea	0 (2.8)	0 (0)	0 (0)	0 (0)	0.1549	<i>0.0097</i>	<i>0.0265</i>
Wellbeing	5 (4)	4 (3)	3 (4)	2 (3.5)	<i>0.0015</i>	<i>0.0003</i>	<i>0.0003</i>
Asthenia	7 (3.8)	5 (5)	3 (7)	3 (6)	<i>0.006</i>	<i>0.0003</i>	<i>&lt;0.0001</i>
Depression	3 (5.5)	0 (5)	0 (0)	0 (0.5)	0.2102	<i>0.005</i>	<i>0.0013</i>
Anxiety	4 (7)	0 (4)	0 (4)	0 (2)	<i>0.0018</i>	<i>0.0033</i>	<i>&lt;0.0001</i>
Insomnia	3.5 (8)	0 (4.3)	0 (0)	0 (0)	<i>0.0009</i>	<i>&lt;0.0001</i>	<i>&lt;0.0001</i>
Appetite	5 (8)	4 (6)	4 (5)	4 (5)	0.2824	<i>0.0503</i>	<i>0.0278</i>
<sup>a</sup> Interquartile range							

Median (range) methadone daily doses at T2 and T7 were significantly higher than that at T0 [7.5 (2.5–19.5) and 6.75 (1.25–21) versus 5 (2.5–10);  $p = 0.0479$  and  $p = 0.0009$ , respectively] (Fig. 2B). The OIE at T7 was 1.7%. The maximum individual dose was 21 mg/day in only 1 patient, and the median (range) number of rescues was 0 (0–3) ( $n = 374$  determinations). Among patients who reached controlled pain, the median (range) stabilization dose was 5 (2.5–17.5) mg/day and the median time for stabilization was 3 (1–5) days.

Between T1 and T7, 39 to 41 patients (63–66%) received laxatives, 28–32 (45–52%) antiemetics, 11–16 (18–26%) corticosteroids, 14–17 (23–27%) benzodiazepines and 14–19 (23–31%) acetaminophen. Other medication included pregabalin, antidepressants, NSAIDs and levomepromazine in 1 to 7 patients (2–11%). Median (range) ECOG performance status score was 2 (1–3) for every time point.

## Discussion

A comprehensive evaluation of the titration phase during first-line methadone treatment of cancer pain is provided. A growing number of studies report the successful use of methadone as a first line opioid [8]. Moreover, it has been proposed that methadone titration might be easier and safer in strong opioid naïve patients than in patients rotated from other strong opioid to methadone [11, 21]. However, a recent revision of these studies concluded that information about the modalities of dose titration is still insufficient [8], with only few studies that partially analyze this phase. For example, Ventafridda and colleagues showed that during the first days, methadone average dose remained unchanged while that of morphine had to be consistently increased [22]. In contrast, another comparative study showed that methadone initially required more up and down changes until dose stabilization than morphine [11]. On the other hand, Bruera and colleagues found a higher rate of dropouts due to opioid-induced side effects (mainly sedation) during titration with methadone than with morphine [21].

The latest reviews in methadone [5, 7] advise a strategy of slow titration without dose increase in the first 5 to 7 days, along with the use of shorter-acting opioid medication for breakthrough pain. Such scheme is based on methadone's pharmacokinetics where the steady state is supposed to be achieved after 5–7 days and it is mainly supported by studies in drug dependence and methadone maintenance therapy [23, 24]. Palat and colleagues have recently described their method for methadone titration in the outpatient setting which allowed dose increases of no more than 5 mg every 5–7 days, according to the patient's response [25].

Our modality for titration allowed early dose increases from Day 1, in accordance with previous reports where the steady state was achieved in less than 5 days [26], together with the use of rescue methadone for breakthrough pain. The feasibility of this more aggressive titration method is based on our previous positive experience [27] and the possibility for a close daily supervision of patients. Using this scheme, we found minimal need for titration and for breakthrough doses, and no evidence of accumulation or sedation by the end of the week. The time to achieve dose stabilization (3 days) was comparable to previous reports [11]. The highest median methadone daily dose administered (7.5 mg/day) was lower than the initial doses used in most of the preceding studies [11, 15, 21, 22, 28–30], and the OEI was similar or lower [11, 30–32]. These findings suggest that the methadone dose remained low and stable over the analyzed period.

In the present study, multiple complementary and strict pain reduction and pain control criteria were used. Pain control was determined through the combination of both numerical and categorical scales. The tolerability scale, on the other hand, relies on the patients' subjective experience of pain alleviation. Sometimes, the patient's tolerance to pain, and not the numerical score, guided the physician's decision to increase the opioid dose. We observed a drastic decrease of the median intensity of pain from 8 to 4 after the first day on methadone, which was paralleled by the other scales. At the individual level, 50 patients (81%) reached pain control, most of them in the first 48 hours, and 36 (58%) reached an intensity of pain they considered still comfortable +/- 1 point. It is worth to say that a substantial percentage of patients (35%) expressed high expectations, with desired values of 0 or 1.

There were two cases of limiting delirium, one of them seemed to be secondary to hypercalcemia. In a previous study, methadone as compared to morphine produced more adverse effects and dropout rate, particularly during the first 8 days [21]. Authors raised the possibility that the relative higher starting doses of methadone (median of 15 mg/day) or the utilization of methadone as a breakthrough opioid may have accounted for the higher toxicity. In this sense, the low methadone doses used in the present study could justify the low toxicity despite the use of methadone rescues. There were also few cases of severe nausea and constipation. In addition to methadone's

lower induction of nausea and constipation in comparison to other opioids [11, 15, 21, 32], there was a substantial prescription of adjuvant laxatives and antiemetics at admission. Other symptoms accounting for the moderate to high initial symptom burden, namely asthenia, wellbeing, and anxiety, also significantly decreased from Day 1.

A considerable percentage of patients (6%) withdrew from the study at their own decision, none of them due to uncontrolled pain. The underlying reasons were the patient's ability or willingness to continue. In addition to the progression of the disease, aversion to opioids for presumed side effects (opiophobia, bad press), reluctance to participating in research protocols, and lack of confidence with a team they were meeting for the first time, may have accounted for this result, and would probably have affected continuity in protocols with other opioids as well.

The major weaknesses of this study include the relatively small sample size and the high rate of patient discontinuation. A high attrition rate is intrinsic to PC trials [34], so being able to access a larger initial sample would be essential. In addition, further studies are necessary to evaluate the OEI and adverse effects beyond the first week with this modality of treatment.

It can be concluded that the first week of treatment with low dose methadone, including the use of methadone for breakthrough pain, and mainly in the outpatient setting resulted in a rapid pain control with no need for significant titration in most patients. Methadone is a desirable alternative for LMIC due to extremely high price of extended-release opioid alternatives. Despite the need for precaution, methadone is frequently the only opioid that can be administered 2- times a day and it is therefore among the most used opioids in our population. Present evidence for a convenient and safe titration can significantly improve its accessibility and help to overcome existing challenges in pain alleviation in these countries.

## Declarations

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**Ethics approval:** The study was approved by the Hospital Tornú Ethical Committee, Buenos Aires, Argentina (No.022/2015).

**Availability of data and material:** All data relevant to the study are included in the article.

**Code availability:** N/A

**Authors' contributions:** Dr. Dran, Bertolino and Mammana have full access to all the data used in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Dran, Bertolino and Mammana participated in the conception and design of the study, the data analysis, and the writing of the manuscript. Dr. Bruera have made substantial contributions to the conception of the study and have critically revised the final and previous versions of the manuscript. Dr. Orellana, Vega, Peirano and Bunge have performed

the material preparation, data collection, and contributed to the analysis and interpretation of data. Mr. Armesto have developed the statistical analysis. All authors read and approved the final manuscript.

**Consent to participate:** All patients gave their informed consent to participate.

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## Figures

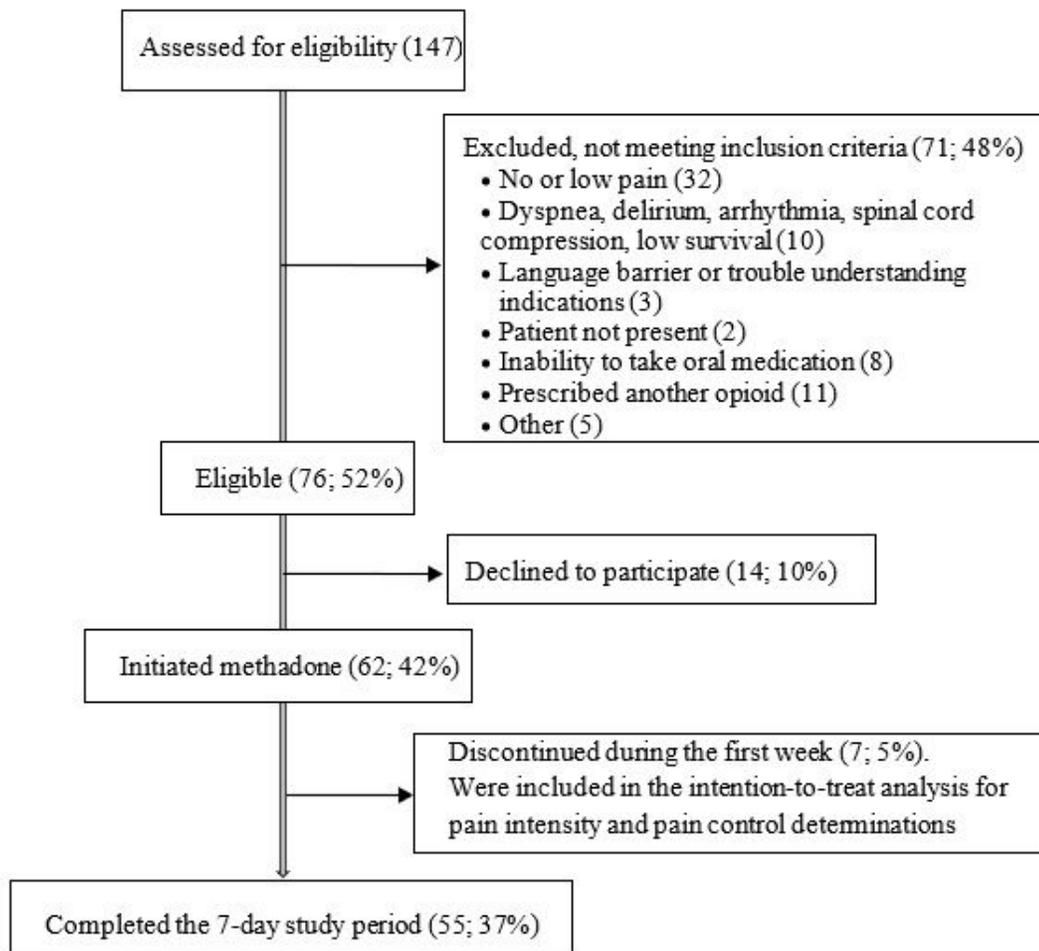
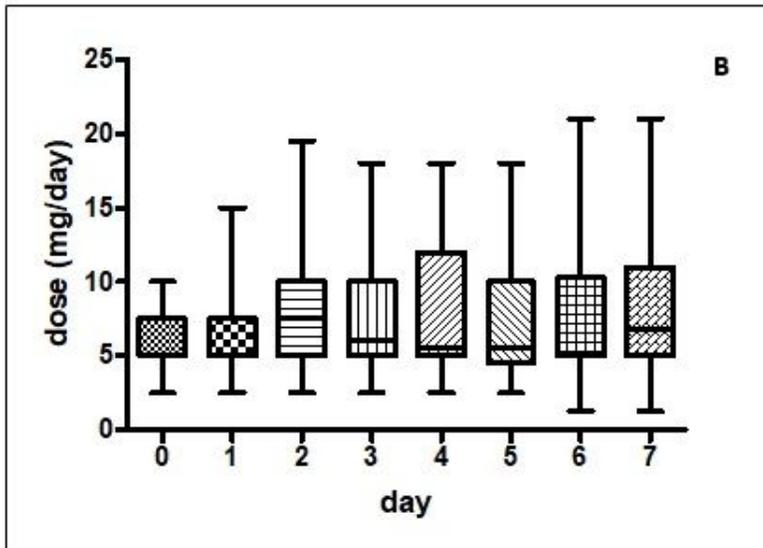
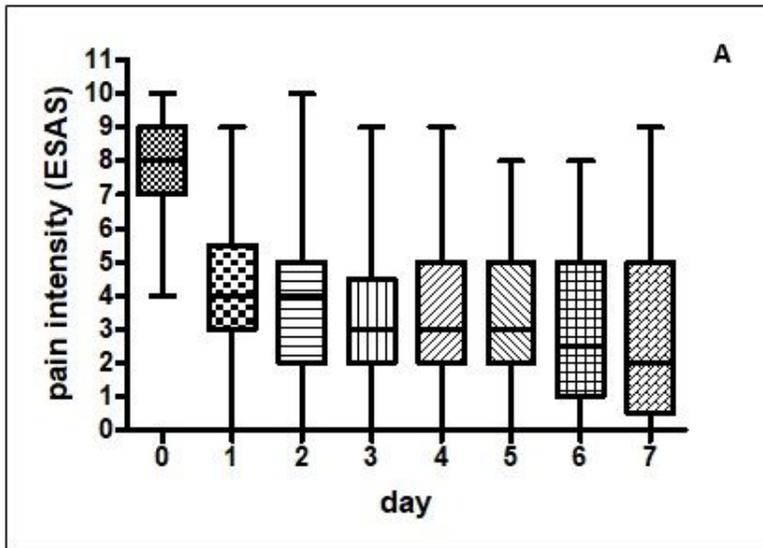


Figure 1

Patient accrual flow chart



**Figure 2**

Variations in pain intensity and in methadone daily dose during the 7-day study period. (A) Median ESAS score for pain significantly decreased from Day 1 (all time points  $p < 0.0001$  compared to baseline). (B) Median methadone daily dose at T2 and T7 were significantly higher than that at T0 ( $p = 0.0479$  and  $0.0009$ , respectively)