Methadone Versus Morphine As a First-Line Strong Opioid for Cancer Pain: A Randomized, Double-Blind Study

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ABSTRACT

Purpose
To compare the effectiveness and side effects of methadone and morphine as first-line treatment with opioids for cancer pain.

Patients and Methods
Patients in international palliative care clinics with pain requiring initiation of strong opioids were randomly assigned to receive methadone (7.5 mg orally every 12 hours and 5 mg every 4 hours as needed) or morphine (15 mg sustained release every 12 hours and 5 mg every 4 hours as needed). The study duration was 4 weeks.

Results
A total of 103 patients were randomly assigned to treatment (49 in the methadone group and 54 in the morphine group). The groups had similar baseline scores for pain, sedation, nausea, confusion, and constipation. Patients receiving methadone had more opioid-related drop-outs (11 of 49; 22%) than those receiving morphine (three of 54; 6%; \( P = 0.019 \)). The opioid escalation index at days 14 and 28 was similar between the two groups. More than three fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8. The proportion of patients with a 20% or more improvement in pain at 4 weeks in the methadone group was 0.49 (95% CI, 0.34 to 0.64) and was similar in the morphine group (0.56; 95% CI, 0.41 to 0.70). The rates of patient-reported global benefit were nearly identical to the pain response rates and did not differ between the treatment groups.

Conclusion
Methadone did not produce superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first-line strong opioid for the treatment of cancer pain.


INTRODUCTION

Cancer is among the most feared chronic illnesses [1], and more than two thirds of patients with metastatic cancer experience pain [2]. The great majority of these patients require opioid analgesics for appropriate pain control [3]. Morphine has been shown to be an effective analgesic, and it is recommended as a first-line opioid in the WHO Cancer Pain Relief Guidelines [4]. However, only level C evidence supports this recommendation, reflecting the paucity of good-quality clinical studies in cancer pain [5].

Morphine undergoes hepatic metabolism and renal elimination [6]. Some of its active metabolites can accumulate in situations such as chronic treatment, dose escalation, dehydration, or renal failure [6,7]. Opioid metabolite accumulation has been considered one of the major causes of opioid-induced neurotoxicity [7,8]. Other opioid agonists such as hydromorphone, oxycodone, or codeine also result in opioid metabolite accumulation [7,9]. Although its manufacture is simple, the price of morphine ranges according to the international price of the poppy, and even the immediate-
release morphine preparation can be prohibitively expensive in developing countries [10]. Other opioid agonists, particularly the slow-release preparations, are generally unaffordable in developing countries [11,12].

Methadone has a number of potential advantages compared with other opioids, including morphine. Methadone is synthetic and easily manufactured. Thus, it could be a good choice of an opioid for first-line cancer pain treatment for low-income populations or in developing countries. Importantly, methadone does not have any known active metabolites and does not undergo significant renal elimination [13]. Another potential advantage of methadone over other opioids is that it has been found to be a relatively potent N-methyl-D-aspartate (NMDA) receptor antagonist [14]. Excitatory amino acids such as NMDA have been implicated in the development of neuropathic pain and opioid tolerance [15,16]. One disadvantage of using methadone is that it has a long and unpredictable half-life, which can make titration difficult to achieve [13,17,18]. Titration might be easier and safer in patients who have not previously received strong opioids [19].

The purpose of this randomized, double-blind study was to determine whether a specific dose and schedule of oral methadone would produce superior analgesic efficacy at 4 weeks compared with a commonly used oral sustained-release morphine regimen for the management of cancer pain in ambulatory cancer patients requiring initiation of strong opioid therapy outside of the United States. We also sought to compare the tolerability of methadone compared with morphine in this setting.

**Study Design**

This double-blind parallel trial was conducted by seven international palliative care groups (Table 1): Argentina, Yugoslavia, Brazil, Columbia, Chile, Australia, and Spain. The Department of Palliative Care and Rehabilitation Medicine at the University of Texas M.D. Anderson Cancer Center (Houston, TX) coordinated the study but did not enroll patients. The institutional review boards of the coordinating institution and all participating institutions approved the protocol.

**Eligibility Criteria and Randomization**

Patient eligibility criteria included poor control of pain caused by advanced cancer necessitating initiation of strong opioids, normal renal function, life expectancy at least 4 weeks as assessed by the investigating physician, normal cognition as defined by the Mini-Mental State Examination adjusted for education and age [20], and written informed consent. Patients were not eligible if they were already receiving strong opioids, radiation therapy for pain control, or antineoplastic therapy expected to produce an analgesic response. All consenting patients were registered in M.D. Anderson’s Clinical Oncology Research System.

The random allocation sequence was generated centrally by computer-generated numbers stratified by center (site) and by neuropathic pain. Each participating center pharmacy received their site-specific randomized sequential assignment numbers, and the treatment allocation code was kept in a sealed envelope and was made available to the treating physicians in case of emergency. Pain was characterized as neuropathic or nonneuropathic according to the judgment of the treating physician regarding the mechanism of pain. Patients, treating physicians, and research staff assessing the outcomes remained blinded to the identity of the opioid until the end of the study.

**Study Plan and Treatment**

Patients were randomly assigned to receive either oral methadone 7.5 mg every 12 hours and methadone 5 mg every 4 hours as needed for breakthrough pain or slow-release morphine 15 mg twice daily and immediate-release morphine 5 mg every 4 hours as needed for breakthrough pain. The capsules containing the drugs were identical. Patients were instructed to take the first dose at 8 AM on day 1 and subsequent doses at 12-hour intervals. The dose of the study drug was increased if the patient received more than two breakthrough doses per day. The dose increase was decided by the investigator after a daily phone or personal assessment during the first 8 days and weekly thereafter. Dose changes were not less than 30% of the daily opioid dose. For patients reporting clinical sedation, the daily dose was reduced by approximately 30%. All supportive medication, such as laxatives, antiemetics, and other drugs, were continued as required during the study period. All nonopioid analgesic drugs were discontinued on admission to the study.

The duration of the study was 4 weeks. Patients were monitored daily for the first 8 days by either phone calls or clinic visits. Patients also underwent assessments in person on days 8, 15, 22, and 29 of treatment. The protocol required that a patient would be removed from the study if pain became intractable, defined as the patient needing six or more breakthrough analgesic doses in a 24-hour period, absence of pain relief after three consecutive dose increases, or the development of a new, severely painful location (for example, a fracture or acute abdominal pain); an acute complication of the cancer or its treatment developed, including sudden acute changes in the patient’s clinical condition, such as sepsis, cardiovascular events, or delirium; the patient was unable to receive two consecutive doses of the regular analgesic because of nausea or dysphagia; or severe opioid-related side effects (such as sedation or nausea) developed.

**Assessments**

The baseline evaluation included a complete history and physical examination. The pain syndrome was assessed clinically...
and by using the Edmonton Staging System for Cancer Pain [21], which had been used previously by these investigators. The intensity of pain, sedation, confusion, nausea, and constipation was measured on a 0 to 10 numerical scale (0, symptom absent; 10, worst possible symptom). In addition to rating of constipation on a numerical rating scale, bowel movements were categorized as absent, small, moderate, or large.

During each of the first 8 days, assessment involved evaluation of pain and other symptoms using the same tools that were used for the baseline measurements. The weekly assessments included assessment of pain, other symptoms, cognitive function, and the global assessment by both the patient and the investigator of overall benefit. Assessment of overall benefit was on a 1 to 7 scale (1, no important benefit; 2, slightly important benefit; 3, some important, consistent benefit; 4, moderately important, consistent benefit; 5, much important, good deal of benefit; 6, very important benefit; and 7, greatly important benefit).

After patients completed the study, opioid escalation indices on days 14 and 28 were calculated as follows:

\[
\text{Day 14 opioid escalation index} = \frac{\text{total dose on day 14} - \text{total dose on day 1}}{\text{total dose on day 1}} \times 100
\]

\[
\text{Day 28 opioid escalation index} = \frac{\text{total dose on day 28} - \text{total dose on day 1}}{\text{total dose on day 1}} \times 100
\]

**Statistical Methods**

Descriptive summaries are provided for patient demographics, reasons for withdrawal from the study, and pain and side effects at each of the time periods examined (Fig 1). Differences between numbers of patients who withdrew overall and according to specific reasons were compared using \( \chi^2 \) tests. Pearson correlation coefficients were used to correlate outcome measures.

The primary objective of the study was to evaluate the difference in pain intensity measured on a 0 to 10 scale comparing the baseline score with the score at week 4 for each study arm. Our sample size calculation was based on having 80% power to detect a 20% difference in the ratio between the baseline and week 4 pain scores with a two-sided significance level of .05 and assuming that the standard deviation of the average difference score would be approximately one half of that score. We sought to enroll 100 patients per study arm. The primary end point and other major outcomes were dichotomized such that patients were considered responders or nonresponders. Missing data could not be ignored;
as such, patients who were inassessable were categorized as non-responders for all dichotomized end points.

In addition to the primary end point, we also evaluated the change in toxicity. A composite toxicity score was calculated as the sum of the following individual symptom items: sedation, nausea, confusion, and constipation. An increase of 20% or greater was considered clinically significant toxicity. We defined patients as having obvious benefit if they were assessable at baseline and at 4 weeks, had a 20% or greater pain response, and did not have a 20% or greater increase in the composite toxicity score. Nonparametric statistics were used to calculate $P$ values (the Wilcoxon rank sum test for continuous and categoric variable combinations, and Fisher's exact test for categoric variables) because of the nonnormal distribution of several variables and the limited sample size at the close of the study. Differences between the methadone and morphine groups between baseline and day 8 were also evaluated for descriptive purposes regarding the pattern of symptom changes.

## RESULTS

A total of 103 patients were randomly assigned to treatment between May 2000 and November 2001 (this was the total patient accrual at the requested time of closure for this study). Forty-nine patients (48%) received methadone and 54 patients (52%) received morphine. Patient clinical and demographic information at baseline are summarized in Table 2. Baseline symptom scores for registered and assessable patients are summarized in Table 3. Before the study, 99 of 103 patients were receiving 143 different analgesics (some patients received more than one drug): nonsteroidal anti-inflammatories in 59 patients, tramadol in 40 patients, codeine in 30 patients, acetaminophen in 13 patients, and dextropropoxyphene in one patient. The type of analgesia did not differ between the morphine and methadone group. During the study, patients received 50 different laxatives (some patients received more than one drug): senna in 28 patients, lactulose in 13 patients, and mineral oil in nine patients. Patients received antiemetics consisting of metoclopramide in 26 cases and cisapride in two cases. Titration of both antiemetics and laxative was allowed. In all instances, patients continued to receive the same antiemetic and/or laxative until day 8.

### Patient Flow

As shown in Figure 1, 92 of 103 patients (89%) were assessable at day 8 and 66 of 103 patients (64%) were assessable at day 29. By day 8, seven of 49 patients (14%) receiving methadone and four of 54 patients (7%) receiving morphine had withdrawn from the study ($P = .13$). By day 29, 20 of 49 patients (41%) receiving methadone and 17 of 54 patients (31%) receiving morphine had withdrawn from the study ($P = .16$). The reasons for withdrawal from the study did not differ significantly (Fig 1). By day 8, six of 49 patients (12%) receiving methadone had withdrawn because of opioid side effects (four because of sedation and two because of nausea), and none of the 54 patients receiving morphine had withdrawn because of opioid side effects ($P = .01$). The number of withdrawals from the study because of opioid side effects was also significantly greater for patients receiving methadone than for patients receiving

### Table 2. Baseline Clinical and Demographic Characteristics by Treatment Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methadone Arm (n = 49)</th>
<th>Morphine Arm (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Age, years</td>
<td>Median</td>
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</tr>
<tr>
<td></td>
<td>Female sex</td>
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</tr>
<tr>
<td></td>
<td>Primary cancer diagnosis</td>
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<tr>
<td></td>
<td>Gastrointestinal</td>
<td>8</td>
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<tr>
<td></td>
<td>Breast</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Gynecologic or genitourinary</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Thoracic</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>15</td>
</tr>
<tr>
<td>Edmonton pain staging, one missing in each group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low risk</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Moderate risk</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>23</td>
</tr>
<tr>
<td>Folstein Mini-Mental Status Examination score $\geq 27$</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>Neoplastic pain component</td>
<td>19</td>
<td>38.8</td>
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<tr>
<td>$\geq 1$ Opioid toxicity symptom score of $\geq 7$</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>Composite opioid toxicity score†</td>
<td>8.94</td>
<td>7.74</td>
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<tr>
<td>Standard deviation</td>
<td>7.7</td>
<td>7.1</td>
</tr>
</tbody>
</table>

*Symptoms were evaluated using an 11-point numerical rating scale (range, 1 – 10).
†Represents the sum of the opioid toxicity items (sedation, nausea or vomiting, confusion, and constipation).
morphine by day 29 (11 of 49 v three of 54; \( P = .02 \)). The opioid side effects resulting in withdrawal of patients receiving methadone by day 29 were sedation, vomiting, and myoclonus (six, three, and two patients, respectively). The opioid side effects resulting in withdrawal of patients receiving morphine by day 29 were vomiting and delirium (two and one patients, respectively). Two patients died while enrolled onto the study (one patient from the methadone group and one patient from the morphine group). Both deaths were a result of disease progression and were counted as treatment failures.

**Day 8 Trends**

Pain and other symptom score differences between baseline and day 8 were compared for both drugs (Table 3). Of note, the development of sedation in the methadone group showed a distinct pattern, with a more delayed onset of symptom severity than in the morphine group (Fig 2). The proportion of patients with a 20% or more improvement in pain expression at day 8 was similar for both groups, with 37 of 49 patients (75.5%; 95% CI, 62% to 89%) in the methadone group and 41 of 54 patients (75.9%; 95% CI, 63% to 89%) in the morphine group.

**Dosing Outcomes**

The daily methadone dose was a median of 17.5 (range, 7.5 to 40 mg) and 20 mg (range, 7.5 to 55 mg) on days 14 and 28, respectively. The morphine dose was a median of 40 (range, 15 to 100 mg) and 45 mg (range, 15 to 150 mg) on days 14 and 28, respectively. The daily breakthrough dose in the methadone group was a median of 0.5 (range, 0 to 15 mg) and 0 mg (range, 0 to 20 mg) on days 14 and 28, respectively, versus 0.5 (range, 0 to 20 mg; \( P = .55 \)) and 0 mg (range, 0 to 80 mg; \( P = .79 \)) for the morphine group.

The opioid dose escalation index for the methadone group was a median of 12.5 (range, −50 to 100) and 18.3 (−50 to 200) on days 14 and 28, respectively, versus 16.7 (range, −14 to 500; \( P = .07 \)) and 16.7 (range, −57 to 900; \( P = .5 \)) for the morphine group. The opioid dose escalation indices in patients with or without neuropathic pain were similar in the morphine and the methadone groups.

**Bowel Movements**

The quantity of bowel movements did not differ at baseline between the two groups. The difference of the number of bowel movements compared with baseline was not different between the groups at any time.

**Day 29 Outcomes**

Patients were categorized as responders or nonresponders for the purpose of evaluating the primary and secondary outcomes (Table 4). The proportion of patients reporting at least moderate global benefit (a score of 4 or greater on the 7-point ordinal scale) was similar to the proportion of pain responders. The proportion of patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Day 8 − Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>7.7 ± 2</td>
<td>7.6 ± 2</td>
</tr>
<tr>
<td>Sedation</td>
<td>2.0 ± 3</td>
<td>2.3 ± 3</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.9 ± 3</td>
<td>2.1 ± 3</td>
</tr>
<tr>
<td>Confusion</td>
<td>0.5 ± 2</td>
<td>0.6 ± 2</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.6 ± 4</td>
<td>4.5 ± 4</td>
</tr>
</tbody>
</table>

Table 3. Comparisons of Symptom Difference Scores From Baseline to Day 8

Fig 2. Mean sedation scores for patients receiving methadone and morphine for baseline through day 8.

Abbreviation: SD, standard deviation.

*Patients who completed the first 7 days of treatment.
†Categorical scale 0–10: 0, best; 10, worst.
with both pain response and stable composite toxicity scores (the obvious benefit group) was half as great as the pain response rate for both treatment groups. Although there were no significant differences between the treatment groups, the final sample size allowed only 0.46 power to detect a 20% difference in proportions. However, it had more than 80% power to detect a 30% or greater difference.

**Correlations Between Outcome Measures**

The patient global satisfaction ratings on day 29 were highly correlated with the physician global ratings ($r = 0.88$).

**DISCUSSION**

Previous studies have provided evidence that methadone is a highly effective second-line opioid for cancer pain [17,22], but this is the first double-blind study of methadone in patients starting strong opioid analgesics. In this international palliative care setting, twice-daily methadone at a total dose of 15 mg/d did not produce superior analgesia for the treatment of cancer pain when compared with sustained-release morphine at a dose of 30 mg/d (along with methadone + immediate-release morphine used for breakthrough pain).

The dropout rate observed in this study was consistent with that observed in other palliative care studies [23], and suggests that both drugs were well tolerated in this population of seriously ill cancer patients. As expected, more than 75% of patients had significant improvement in pain with either strong opioid during the first week of treatment. However, when inassessable patients were incorporated as nonresponders, the overall pain response rate at 4 weeks using oral opioids was surprisingly low for both morphine and methadone in this first-line setting. It should be noted, however, that a significant number of the inassessable patients at day 29 may have obtained adequate pain relief ultimately with comprehensive medical pain management, but were removed from this protocol for reasons such as frequent dose escalation or inadequate pain response after three dose escalations. Opioid-related treatment outcomes are reported in many different ways, and thus it is difficult to compare these findings with other randomized trials of first-line opioids. It has been noted that as many as 80% of cancer patients require one switch in their analgesic regimen and as many as 44% require trials of two or more systemically administered opioids [24]. Perhaps these data are not surprising, then, if one assumes that patients need to switch analgesic regimens because of inadequate pain relief, unacceptable side effects, or the unacceptably high cost of therapy.

Although there were no differences in the major response or toxicity outcomes at 4 weeks, the dropout rate because of opioid side effects was higher for methadone than for morphine at both days 8 and 29. This suggests that the true dose ratio between methadone and morphine may be lower than the ratio of 0.5 (7.5:15) we used in this study. Moreover, it also is possible that methadone is more toxic than morphine when it also is used as a breakthrough opioid. Future research should consider this issue. Half of the patients who received methadone and dropped out of the study because of opioid side effects did so during the first 8 days. This indicates the need for close monitoring of patients in the first week after initiation of methadone at this dose and schedule.

There are few data on which to base the initial dosing of methadone for cancer pain in patients not already receiving a strong opioid. The equianalgesic dose of 1:2 (methadone-to-morphine ratio) for the regularly scheduled part of the opioid regimen was chosen on the basis of published opioid rotation data with patients receiving oral morphine at low doses [17,25,26]. Our findings suggest that methadone given every 12 hours resulted in good pain control, but it was not superior to the morphine regimen. This particular methadone regimen is different from the 8-hour regimen reported most fre-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Responders</th>
<th>% of Responders</th>
<th>95% CI (%)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Pain response of 20% or greater</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>24</td>
<td>49</td>
<td>34 to 64</td>
<td>.50</td>
</tr>
<tr>
<td>Morphine</td>
<td>30</td>
<td>56</td>
<td>41 to 70</td>
<td>.94</td>
</tr>
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<td>Composite toxicity worse by 20% or more</td>
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<td>Methadone</td>
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<td>67</td>
<td>53 to 82</td>
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<td>Morphine</td>
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<td>67</td>
<td>53 to 80</td>
<td>.94</td>
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<td>Pain response with stable composite opioid toxicity (obvious benefit)</td>
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<tr>
<td>Methadone</td>
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<td>24</td>
<td>11 to 38</td>
<td>.56</td>
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<tr>
<td>Morphine</td>
<td>16</td>
<td>30</td>
<td>16 to 43</td>
<td>.56</td>
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<td>Patient-reported global benefit (at least moderate)</td>
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<td>.41</td>
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<td>Methadone</td>
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<td>.41</td>
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<tr>
<td>Morphine</td>
<td>33</td>
<td>61</td>
<td>47 to 75</td>
<td>.41</td>
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the mu-opioid morphine but not to the kappa opioids. Pain 56:69-75, 1994