

# Starting Step III opioids for moderate to severe pain in cancer patients: Dose titration: A systematic review

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**Pål Klepstad** *Pain and Palliation Research Group, Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Department of Intensive Care, St Olavs University Hospital, Trondheim, Norway*

**Stein Kaasa** *Pain and Palliation Research Group, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Department of Palliative Care, St Olavs University Hospital, Trondheim, Norway*

**Petter C Borchgrevink** *Pain and Palliation Research Group, Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; Center for Pain and Complex Disorders, St. Olav University Hospital, Trondheim, Norway*

## Abstract

The European Association for Palliative Care recommendation for starting morphine for cancer pain is dose titration with immediate release (IR) oral morphine given every 4 h with additionally doses for breakthrough pain. As part of a EU 6th framework programme to revise the guidelines we review the evidence regarding starting treatment and dose titration of opioids in adult patients with moderate to severe cancer pain. Relevant papers were identified through a systematic search in Medline for papers published until the end of 2009. We identified 15 relevant papers. Thirteen papers were descriptive papers reporting the results from starting treatment with oral morphine (six studies), starting treatment with intravenous morphine (two studies) and starting treatment with transdermal fentanyl (four studies). All treatment strategies resulted in acceptable pain control and were well tolerated. Two randomized controlled trials were identified. One study compared starting opioid treatment with intravenous morphine versus IR oral morphine and one study compared IR oral morphine versus sustained release oral morphine.

## Keywords

Neoplasm, pain, opioids, titration, starting treatment

## Introduction

The leading principle for pain management of cancer pain today is the World Health Organization (WHO) pain ladder.<sup>1</sup> The WHO pain ladder is based on a three-step approach for pain treatment. Step one is the use of non-opioids such as paracetamol or NSAIDs. Step two escalates treatment to the use of an opioid for mild to moderate cancer pain combined or not combined with a non-opioid analgesic. If pain persists or increases despite administration of a step-two opioid, the pain treatment is changed to an opioid for moderate to severe cancer pain.

The European Association for Palliative Care (EAPC) has published detailed recommendations for the use of opioids for treatment of cancer pain. The guideline was first presented in 1996 and a revised

version of the guidelines was published in 2001.<sup>2,3</sup> The recommendations are based upon scientific evidence, or if evidence is not available, upon consensus from a European expert panel. The recommendations are summarized into 20 specific treatment advices for the administration of opioids to patients with cancer pain. The 2001 guidelines categorized the scientific level of evidence for each specific advice. These evaluations show that, to a great extent, the treatment for cancer pain is not methodologically tested in prospective trials, but based upon experience or expert opinions.

The procedure for starting treatment morphine is stated in EAPC recommendation no 3.

‘The simplest method of dose titration is with a dose of normal release morphine given every 4 hours and the

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## Corresponding author:

Pål Klepstad, Department of Intensive Care Medicine, University Hospital of Trondheim, N-7006 Trondheim, Norway  
Email: pal.klepstad@ntnu.no

same dose for breakthrough pain. The rescue dose may be given as often as required (up to hourly) and the total daily dose of morphine should be reviewed daily. The regular dose can then be adjusted to take into account the total amount of rescue morphine.'

This recommendation was defined at a level of evidence C, which is evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.<sup>3</sup> Other guidelines, including the US counterpart of the European guidelines for treatment of cancer pain, the Agency for Health Care Policy and Research Guidelines for Cancer Pain Management, follows similar principles for initiation of opioid treatment.<sup>4</sup>

The most recent revision of the EAPC guidelines was published in 2001. The appropriate lifetime for guidelines is not established, but a general rule of 3 years between reassessments has been proposed.<sup>5</sup> The time-frame since the last revision of the guideline and additional available evidence initiated a programme supported by the EU 6<sup>th</sup> framework to revise the guidelines for opioid treatment of cancer pain. Through a Delphi process, each current recommendation was evaluated for inclusion into a new revised set of recommendations, and additional novel issues that should be addressed by an opioid treatment guideline were identified.<sup>6</sup> For each proposed issue to be addressed in the new guidelines, a systematic review was performed in order to obtain information about the current state of evidence and to propose new recommendations.

The aim of this paper is to present a systematic review for the recommendation regarding the start of treatment with opioids and dose titration in adult patients with moderate to severe pain due to cancer and who are not exposed to strong opioids. The questions were: what is the evidence for optimal titration in terms of the initial dose, titration schedule, route of administration, and the choice of opioid formulation (immediate or slow release).

## Methods

Relevant papers were identified through a systematic search in Medline for papers published until the end of 2009 using the following search strategy:

Search #1 titration OR start.

Search # 2 palliative care OR cancer OR malignant.

Search #3 opioid OR morphine OR fentanyl OR oxycodone OR hydromorphone OR buprenorphine OR methadone.

Search #4 pain

Search #1 AND #2 AND #3 AND #4 Limits Humans, English.

We defined no start date for the search, thereby including all eligible papers in Medline. The papers identified by this search strategy were reviewed by one of the authors (PK) and relevant papers were identified. These references were hand-searched in order to find additional relevant papers, resulting in the inclusion of one paper not identified by our search strategy, by Kumar et al.<sup>7</sup> which was included in a review of opioid dose titration by Davis et al.<sup>8</sup> Relevant papers were those specifically addressing the initiation of opioid treatment for the treatment of cancer pain, with the exception of papers addressing issues handled by other parts of the guidelines development programme. This included papers comparing different opioids, papers describing dose adjustments of ongoing treatment for patients using an opioid for moderate to severe cancer pain, and papers addressing start of a second-line opioid for moderate or severe cancer pain. Finally, the ongoing debate around the use of 'weak' opioids or low-dose 'potent' opioids in the management of moderate (Step II) pain was not included in this review but is the subject of another systematic review.

The randomized controlled trials identified were assessed following the recommendation from the GRADE working group.<sup>9</sup> The details of the observational and the randomized controlled trials are summarized with respect to interventions, assessments, number of patients and observations.

## Results

The search strategy resulted in 230 hits; from titles and abstracts, 19 relevant papers were selected. Eight papers were not relevant as they included patients with ongoing opioid treatment for moderate or severe cancer pain (WHO step III opioid). In addition, by hand-searching or identifying in a related review, four more relevant papers were identified resulting in a total number of 15 relevant papers. Thirteen papers were descriptive papers reporting the results from one specific method for initiation of opioid treatment. The described methods were starting treatment with oral morphine (six studies, of which two reported observations from the same population), starting treatment with intravenous morphine (three studies) and starting treatment with transdermal fentanyl (four studies). The general findings from all studies were that all treatment strategies resulted in acceptable pain control and were well tolerated. Some of the details from each of these studies are given in Table 1. Only two randomized controlled trials on research questions addressing methods

Table 1. Identified descriptive papers

Author	Year	N	Drop-out	Pain assessment	Side effects assessment	Study and primary findings
Gatti et al. <sup>16</sup>	2009	72	9	NRS 0–10	Patient self report	Titration with IR morphine and switch to SR morphine. Start dose 5 mg every 4 h in opioid-naïve patients and 10 mg every 4 h in patients using a step II opioid. Acceptable pain control (90% more than 50% pain reduction) and well tolerated.
De Conno et al. <sup>17</sup>	2008	159	24	NRS 0–10	3-point VRS by investigator	Titration with IR morphine. Start dose 5 mg every 4 h in opioid-naïve patients and 10 mg every 4 h in patients using a step II opioid. Acceptable pain control (pain NRS decrease from 7.6 to 1.7 after 5 days. Well tolerated with initial adverse events that resolved.
Ripamonti et al. <sup>18</sup>	2009	159	28	NRS 0–10	Not reported	Extension of analyses performed on the same patient population as described by de Conno et al. <sup>17</sup>
Tawfik et al. <sup>19</sup>	2004	157	11	VAS 0–100 mm	4-point VRS by patient and investigator	Titration with transdermal fentanyl, start dose 25 µg/h. Acceptable pain control (pain VAS decrease from 60 to 35). Five patients were withdrawn due to treatment-related adverse effect.
Mercadante et al. <sup>20</sup>	2002	30	3	NRS 0–10	4-point VRS	Titration with iv morphine 2 mg every 2 min. After titration converted to equianalgesic oral morphine doses. Pain control after a mean time of 9.7 minutes. Increase in number of patients experience drowsiness, confusion and emesis, but generally well tolerated.
Mystakidou et al. <sup>21</sup>	2001	130	14	NRS 0–10		Titration with transdermal fentanyl, start dose 25 µg/h. Acceptable pain control (Pain NRS decrease from 6.0 to 0.8 after 3 days. Nine patients stopped treatment due to adverse effects or lack of effect.
Radbruch et al. <sup>22</sup>	1999	28	2	NRS 0–10	4-point VRS	Titration with iv morphine using patients controlled analgesia. Dose 1 mg, lockout-time 5 min. Conversion to oral morphine day 2. Adequate pain relief after a mean time of 5 h. Incidence of adverse effects did not change between baseline and day 14.
Klepstad et al. <sup>23</sup>	2000	40	6	VAS 0–100 mm and 7-point VRS	VAS 0–100 mm or 4-point VRS	Titration with IR morphine. Start 10 mg every 4 h in patients using a step II opioid. Acceptable pain control after a mean time of 2.3 days. Increase in constipation while other adverse effects unchanged.
Korte et al. <sup>24</sup>	1996	18	Not reported	VAS 0–100 mm	Not reported	Titration with transdermal fentanyl, start dose 25 µg/h. Acceptable pain control (pain VAS decrease from 54 to 22 after 7 days). Nausea reported by 69% of the patients, but uncertain aetiology.
Vijayaram et al. <sup>25</sup>	1990	223	43 at day 10	Local 'Ruppee scale'	Not reported	Titration with oral morphine mixture. Acceptable pain control after a mean time of 4 days. Nausea reported in 48 patients at day 10. Well tolerated.
Mercadante et al. <sup>26</sup>	2006	110	15	NRS 0–10	4-point VRS	Titration with IR morphine to opioid-naïve patients. Start 15 mg/24h divided in 4–6 doses. Acceptable pain control (pain NRS decrease from 6.1 to 3.2 after 1 week). Well tolerated besides an increase in constipation and dry mouth.
Vielvoye-Kerkmeier et al. <sup>13</sup>	2000	28	9	NRS 0–10	Patient self-report	Titration with transdermal fentanyl, start dose 25 µg/h. Acceptable pain control pain (19 patients rated pain treatment as good or excellent). Four patients stopped treatment due to adverse effects.
Kumar et al. <sup>7</sup>	2000	491	Study of case notes	NRS 0–10 or five-point VRS	As reported in case notes	Titration with iv morphine 1.5 mg every 10 min. 79% had 'total pain relief'. One-third experienced drowsiness. Otherwise well tolerated.

<sup>a</sup>Numbers of patients in the study reported to be naïve to opioids for moderate or severe cancer pain (step III opioid).

IR morphine, immediate-release oral morphine; SR morphine, slow-release oral morphine; NRS, numeric rate scale; VAS, visual analogue scale; VRS, verbal rate scale.

Table 2. Identified randomized trials

Author	Year	Study groups	N	Drop-out	Pain assessment	Side effect assessment	Study characteristics	Outcomes
Harris et al. <sup>10</sup>	2003	A. IV titration with 1.5 mg morphine every 10 min. After pain control converted to equi-analgesic dose of oral morphine. B. Titration with IR morphine. Start dose 5 mg every 4 h in opioid naïve patients and 10 mg every 4 h in patients using a step II opioid.	62	10	NRS 0–10	Not reported	Prospective Randomized Not blinded No sample size calculation	Faster onset of pain relief using iv morphine (27/31 vs. 8/31 for adequate pain relief after 1 h) After 24 h similar pain relief in both groups. 11 patients reported drowsiness after iv titration. No serious adverse effects
Klepstad et al. <sup>11</sup>	2003	A. Titration with IR morphine. Start dose 10 mg every 4 h in patients using a step II opioid. B. Titration with SR morphine. Start dose 60 mg every 24 h opioid.	40	6	VAS 0–100 mm and 7-point VRS	4-point VRS	Prospective Randomized Double blind Double dummy Sample size based on a clinical difference of interest of 1.5 days for titration	Similar onset of pain relief (2.1 vs. 1.7 days) Both treatments well tolerated with no differences in adverse effects between the study groups or compared with baseline

IR, morphine, immediate-release oral morphine; SR, morphine, slow-release oral morphine; NRS, numeric rate scale; VAS, visual analogue scale; VRS, verbal rate scale.

**Table 3.** GRADE assessments for randomized controlled trials

No of studies	Quality assessment						Quality		Ref
	Design	Quality	Consistency	Directions	Other factors	Number of patients in each study arm			
Start of oral opioid treatment with immediate release opioids versus sustained release opioids (days to titrated dose)									
1	Randomized controlled trial	No serious limitation	NA	No uncertainty	Adequate data	20	20	Moderate	Klepstad et al. <sup>11</sup>
Start of opioid treatment with oral versus intravenous opioids (number of patients with pain relief after 1 h)									
1	Randomized controlled trial	Serious limitations Not blinded No sample size estimation	NA	No uncertainty	Sparse data	31	31	Low	Harris et al. <sup>10</sup>

for initiating treatment with opioids for moderate to severe pain were identified. One study compared the start of opioid treatment with intravenous versus immediate release oral morphine,<sup>10</sup> and one study compared immediate-release oral morphine versus sustained release morphine.<sup>11</sup> The details for the two studies are given in Table 2. The quality as assessed by the GRADE framework<sup>9</sup> of the two studies was low and moderate for the intravenous versus immediate-release oral morphine<sup>10</sup> and the immediate release oral morphine versus sustained release morphine<sup>11</sup> study, respectively (Table 3).

Due to the low number of identified studies and the high diversity of methods, no statistical analyses merging findings from studies were employed.

## Discussion

This review shows that the evidence guiding how to start opioid treatment for cancer pain is limited. Only two randomized controlled trials were identified, one comparing intravenous versus oral morphine titration and one comparing titration with immediate-release morphine versus titration with sustained release morphine. In addition, 13 descriptive studies reporting the feasibility of titration with oral immediate release morphine, intravenous morphine and transdermal fentanyl were found.

The initiation and titration of an opioid for moderate and severe pain is a critical point during individual patient treatment. The time to start opioid treatment is often associated with progressive disease, and most patients receive several other treatments. Also, by definition the pain itself is not controlled. The experience of pain is a direct burden on the patients' total situation and the patients will, often rightly, interpret increased pain as a sign of disease progression. This unstable

clinical setting during the start of opioid treatment argues that results obtained in patients on stable opioid therapy are not necessarily representative for patients when commencing opioid treatment. Another principal difference between patients when starting morphine treatment and those on long-term treatment is that tolerance to adverse effects has yet to develop at the start of opioid administration. Bruera et al. showed that escalations of opioid doses increased cognitive impairment.<sup>12</sup> The cognitive impairment associated with dose increments disappeared after 1 week. Bruera et al. also observed that drowsiness and nausea are more pronounced after morphine dose adjustments.<sup>12</sup> The importance of opioid tolerance and side effects with opioids is also illustrated by Vielvoye-Kerkmer et al.<sup>13</sup> They observed that adverse effects after starting treatment with of fentanyl patches (25 µg/h) were more frequent in opioid-naïve patients than in patients previously consuming codeine.

Despite the frequent and widespread use of opioids for cancer pain, few studies have assessed optimal initial doses in the opioid naïve. The descriptive papers summarized in Table 1 show that opioid treatment can be adequately and safely started with a number of therapeutic approaches, including titration with immediate-release morphine, titration with intravenous morphine and titration with transdermal fentanyl. The two randomized trials identified in this review demonstrate the importance of performing studies comparing strategies for start of opioid treatment. The study by Harris et al. shows that if fast onset of pain relief is crucial, titration with intravenous morphine is more efficient than oral morphine.<sup>10</sup> The study by Klepstad et al. shows that for patients escalating pain treatment from WHO step II to WHO step III, titration of the opioid dose using once-daily sustained oral morphine is as efficient as 4-hourly oral immediate release morphine.<sup>11</sup> This finding

argues against the EAPC guideline recommendation of titration with oral immediate release morphine given 4-hourly.<sup>2,3</sup> The argument in the EAPC guideline in favour of immediate release morphine titration is to allow for steady state as quickly as possible in order to ease the assessment of adequacy of analgesia during the dose-finding period and to make rapid changes in dose.<sup>2</sup> However, the use of 5–6 daily scheduled morphine doses is cumbersome and may reduce patient compliance.<sup>14</sup> Also, patient perception of overmedication (‘taking a higher number of tablets that are administered more frequently’) is associated with decreased compliance.<sup>15</sup> With the use of controlled-release morphine during titration, the patients are spared a multiple-dose schedule, and this decreases patients’ perception of being over ‘medicated’. A direct start with controlled-release morphine could simplify the treatment, reduce the risk of low compliance, and thereby enhance efficacy.

The limited number of controlled studies identified in this review precluded a formal meta-analysis summarizing findings from various studies. The formal GRADE assessments of the two randomized studies also showed that the quality of the two studies was assessed as low and moderate, respectively. Therefore, until more studies are performed, the evidence regarding issues related to starting of opioid treatment is based upon one single randomized trial of low or moderate quality, descriptive studies or expert opinions.

In conclusion, the answers to the four key questions related to starting opioid treatment for cancer pain patients are:

What is the optimal initial dose for titration of opioids in adult patients with pain due to cancer? *Given the present available knowledge, descriptive studies demonstrate that starting with oral morphine 30 mg/24 h in opioid-naïve patients and 60 mg/24 h in patients using a WHO step II opioid is safe and efficient. Descriptive studies also demonstrate that starting with transdermal fentanyl 12.5–25 µg/h is feasible. However, recommendations must be at the present stage be based on descriptive studies and expert opinions.*

What is the optimal schedule for dose increase during titration of opioids in adult patients with pain due to cancer? *Given the present available knowledge there is no evidence to decide recommendations of schedules for dose increases during opioid titration. A recommendation must at the present stage be based on descriptive studies and expert opinions.*

What is the optimal administration route for titration of opioids in adult patients with pain due to cancer? *Given the present available knowledge, oral opioid titration and to intravenous opioid titration are equally effective. However, if it is important to*

*achieve pain control fast (within hours) intravenous titration is more effective.*

What is the preferred formulation between slow and immediate-release formulation for titration of opioids in adult patients with pain due to cancer? *Given the present available knowledge, there is evidence for that oral opioid titration can be performed with oral slow-release opioid formulations.*

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### Competing interests

The authors declare that they have no competing interests.

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