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The MERITO Study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during 'titration phase' in patients with cancer pain

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Adequate and rapid pain control is one of the main goals of cancer pain treatment. The objective of this study was to assess the effect and tolerability of oral normal-release morphine during the initial phase of treatment in patients with moderate-to-severe cancer pain. Consecutive patients naïve to strong opioids received normal-release morphine 5 or 10 mg every 4 h during the titration phase (first 5 days), depending on previous analgesic therapy. Pain intensity was assessed using an 11-point Numerical Rating Scale (0–10), and data were recorded in a patient-compiled diary. The primary endpoint was the proportion of time with pain control (a reduction of at least 50% with respect to the baseline pain score) during the titration phase. A total of 159 consecutive patients (102 men; mean age 65 years) with cancer-related pain were enrolled. Pain control was observed for 75% (95% CI 70–80) of the follow-up period in the intent-to-treat population. Overall, 50% and 75% of patients achieved pain control within 8 and 24 h after starting normal-release morphine therapy respectively. The mean pain score was 7.63 points at baseline, and decreased to 2.43 and 1.67 points (both $P < 0.00$ 1) at days 3 and 5 respectively. The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%). Normal-release morphine results in rapid and satisfactory pain control, and is well tolerated, during the strong-opioid titration phase in patients with moderate-to-severe cancer pain. *Palliative Medicine* (2008); **22**: 214–221

Key words: cancer pain; morphine; normal release; oral; tolerability

Introduction

Morphine is considered to be the strong opioid drug of choice for the management of patients with moderate-to-severe cancer pain because it has a wide therapeutic range, is effective in many routes of administration, available in most countries and is relatively inexpensive.[1–3] The World Health Organization (WHO) has requested that oral morphine is made part of the essential drug list, and made available throughout the world as a treatment for cancer pain.[4] In many countries, morphine is available as a normal, normal-release and as a modified-release formulation, prepared according to different sustained-release mechanisms. In 1996, the Expert Working Group of the European Association for Palliative Care (EAPC) published recommendations on the use of this drug.[5]

Although, some clinicians advocate the use of sustained-release morphine when initiating morphine therapy in cancer patients, numerous recommendations[1–8] in the literature suggest that the best approach to moderate-severe cancer pain is to tailor the dosage of the opioid to the needs of the individual patient, starting treatment with oral normal-release morphine (NRM) because its dosage can be modified every 4 h according to the patient's needs. Once the effective morphine dosage is achieved using the immediate-release formulation, it can be switched to a sustained-release preparation using a proper dosage conversion, with NRM as rescue dose for breakthrough pain.[9] In this way, after an adequate pain assessment, it is possible to titrate and retitrate the opioid dosage needed to achieve pain relief in an individualized way, on a day-by-day basis.

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The WHO has developed a three-step analgesic ladder guideline for the management of cancer pain; here, analgesia is administered by the mouth[10] 'by the clock', rather than on an 'on-demand' basis to maintain freedom from pain.

According to the EAPC recommendations,[5] and to the recent publication by the Italian Ministry of Health,[8] which reiterates guidelines of the British National Formulary,[11] the initial dose of oral morphine should be chosen on the basis of previous treatment. The initial dose of NRM for patients already treated with an opioid for mild-to-moderate pain (WHO analgesic ladder step II) administered according to a time schedule (with or without non-opioid therapy) is 10 mg every 4 h. If a non-opioid therapy was used previously (i.e. step II of the analgesic ladder has been skipped), NRM 5 mg every 4 h is considered to be the appropriate starting dose.

In view of the absence of a plateau effect with morphine, it may be stated that a maximum dosage for this drug does not exist, provided that it is properly titrated, unless adverse events that cannot be managed with specific therapeutic measures appear. The last daily dose of NRM may be doubled (double bedtime dose), thus avoiding the waking up of the patient during the night.[1,5,12]

In contrast to other countries, the use of oral morphine in Italy has been decreasing over the last few years in favour of mild opioids, such as codeine and tramadol,[13] and strong opioids, such as the fentanyl patch, are frequently being administered as first-line therapy even in patients who are able to receive strong opioids orally.[14–16] This approach is inappropriate according to international recommendations,[5,6] which indicate that NRM should be used as first-line therapy, and a recent warning released by Janssen[17] regarding the use of transdermal fentanyl.

The primary objective of the MERITO (Morphine Rapid Effect in Initial Treatment in Oncology) study was to estimate the percentage (proportion) of time with pain control (reduction in pain intensity of at least 50% vs. baseline) during the first 5 days of treatment with oral NRM, administered according to the recommendations of international and national guidelines, in a large sample of Italian patients with advanced cancer and moderate-to-severe cancer-related pain. Secondary objectives were to evaluate the time needed to reach pain control and the tolerability of NRM.

Materials and methods

Patients

From 1 October 2003 to 3 August 2005, 16 palliative care centres in Italy were involved in an uncontrolled, open-label, phase IV clinical trial, which enrolled all consecutive patients who met the followed predefined eligibility criteria:

1) age 18 years or over;
2) pain score of ≥5 points for at least 24 hours, according to an 11-point NRS, where 0 = no pain and 10 = the worst pain possible;
3) naïve to morphine and other strong opioids available in Italy (fentanyl, buprenorphine, oxycodone and methadone), i.e. currently receiving treatment with WHO step I analgesics (non-opioid analgesics for mild pain) or step II analgesics (opioid analgesics for mild-to-moderate pain),[2,3] correctly administered according to WHO guidelines;
4) adequate hydration according to the outcome of a clinical examination;
5) written informed consent.

We escluded from the study the patients who presented the follow conditions:

1) known hypersensitivity to morphine;
2) acute abdomen or paralytic and/or mechanical ileus;
3) MMSE score of <6;
4) history of alcoholism;
5) presence of dyspnoea ,or renal or hepatic failure;
6) ongoing treatment with one of the following therapies: monoamine oxidase inhibitors, tricyclic antidepressants, benzodiazepines or barbiturates, cimetidine or ranitidine;
7) radiotherapy administered within 15 days of study entry.

Pharmacotherapy

Eligible patients received oral NRM sulphate at a starting dose of 5 or 10 mg every 4 h. NRM 5 mg every 4 h was the starting dose for patients with moderate-to-severe pain not controlled with WHO step I analgesics (non-steroidal anti-inflammatory drugs or paracetamol), whereas 10 mg every 4 h was the starting dose for patients receiving step II therapy (codeine plus paracetamol, tramadol). NRM was administered at 07:00, 11:00, 15:00 and 19:00 hours and again at bedtime. A double dose was administered at bedtime to avoid nocturnal dosing.

Patients who did not experience satisfactory pain relief during the interval between one dose and the next could take rescue doses of oral NRM, up to a maximum of one dose every hour; rescue NRM doses were the same as the patient's regular doses. The dosage was retitrated on a daily basis, so that the dosage of oral NRM to be given in the next 24 h was based on the total opioid dose (regular plus rescue) taken by the patient. No maximal dosage limit was imposed by the protocol, unless adverse events

that could not be easily controlled arose. The patients, if possible, had an ambulatory visit after 2 and 5 days from the beginning of the study. On the other days, they received a telephone call to monitor the intensity of pain, the dosage of drug and the onset of other symptoms.

Assessments

At the first visit (T0), patient eligibility was assessed by evaluating pain intensity during the visit and during the last 24 h (according to an 11-point NRS, where 0 = no pain and 10 = the worst pain possible), as well as the type of pain experienced (nociceptive pain, neuropathic pain or mixed pain). Patients received a diary where they (or caregiver, in case of patient inability) recorded pain intensity compared with the preceding 4-h period at each NRM administration, by answering the question 'On a scale of 0–10, where 0 = no pain and 10 = the worst pain possible, how do you rate the intensity of your pain during the last 4 h?' five times daily and recorded their answers in the diaries. Additionally, any changes in the morphine dosage, administration of any adjuvant analgesic therapy, NRM-related adverse events, and the presence and frequency of episodic pain were recorded.

The primary endpoint of this trial was the proportion of time spent during the 5-day titration period with pain control, defined as a reduction of at least 50% with respect to the baseline pain score. The safety of NRM was assessed at each visit by the physician, who recorded any adverse events starting during the 5-day treatment period; using an intensity scale from 1 to 3 (1 = mild; 2 = moderate; 3 = severe).

Sample size

Assuming a normal distribution with a mean of 60 (SD 30) points for the primary endpoint, a sample size of 250 patients would allow an estimate of the two-tailed 95% CI with a width of 6.2 (±3.1), corresponding to a precision of about 10% of the estimated mean level.

Due to organizational problems (reduction in the number of participating centers, from 25 as indicated in the protocol to 16 actually participating, and various difficulties in recruiting patients), the study was stopped before the 250 patients indicated by the protocol were accrued. In the hypothesis formulated for sample size calculations, a sample size of 150 patients allows an estimate of the 95% two-tailed CI with a width of 9.6 (±4.8), which corresponds to a precision of approximately 16% of the estimated mean level. If we compare this level of precision with the 10% indicated in the protocol, we can claim that the sample size reduction led to a limited reduction in the estimated precision.

Data analysis

The intent-to-treat (ITT) population was defined as all enrolled patients who took at least one dose of the study drug, excluding all those who did not fill in any diary entries. The per-protocol (PP) population consisted of all patients enrolled in the study, excluding those for whom major protocol deviations were recorded. Major protocol deviations were defined as: (a) failure to take any doses of the study drug and (b) completion of <20% of the expected diary evaluations (<5 evaluations). The 'safety' population included all the enrolled patients who had taken at least one dose of the drug studied.

Effect data analyses will be performed both on the ITT and the PP populations, whereas safety analyses will be performed in the safety population.

The summary measure approach[18] was applied for the analysis of the repeated measurements of the primary outcome variable (pain intensity evaluated five times daily through a diary). For each patient, the percentage of the follow-up period with pain control was calculated using the following formula:

$$\left(\frac{\mathrm{NVAL_{con}}}{\mathrm{NVAL_{tot}}}\right)\times 100$$

where $\mathrm{NVAL_{con}}$ is the number of post-treatment evaluations with pain control and $\mathrm{NVAL_{tot}}$ is the total number of follow-up evaluations for that patient (25 or less); evaluations collected at 07:00 hours were given a double weighting because they refer to the previous 8 h rather than 4 h, as the case for all the other measurements.

To better describe the way in which pain was controlled, the median time to pain control and the proportion of patients reaching it within the first 24 h were estimated. The estimation was performed using the Kaplan–Meier method and the failure function was displayed.

T-test for paired data was applied to test the significance of pain reduction with respect to baseline on days 3 and 5 of treatment. Box plots of pain scores at different visits (baseline, and days 3 and 5) are also presented.

When primary outcome data were missing, the calculation was performed on an 'available data' basis, calculating the percentage of the follow-up period with pain control for those patients who had completed at least one post-treatment evaluation; in contrast, patients who did not complete any diary evaluations were not included in the analysis. An estimate of the overall compliance for the patients enrolled (number of evaluations completed out of the 25 expected) was presented as average in all patients analysed. When secondary outcome data were missing, the patients with missing data related to a specific variable were eliminated from the analyses involving that variable.

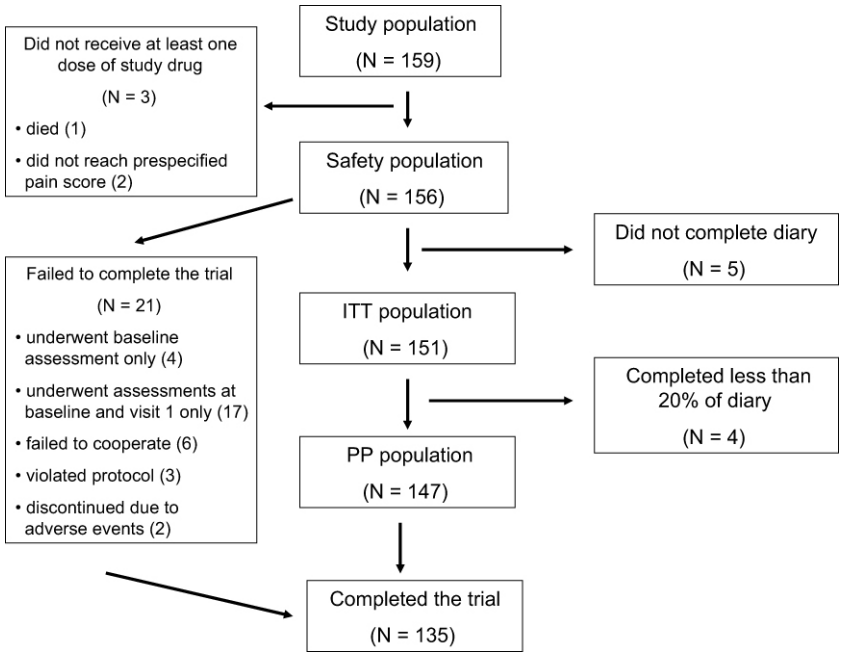

Figure 1 Flow chart describing patients' progress through the trial.
N = number of patients; ITT = intent to treat; PP = per protocol. Adverse events leading to premature treatment withdrawal were somnolence and sedation.

Results

A total of 159 patients, all Caucasian, were enrolled in the study; the flow of patients through the trial and details of drop-outs are shown in Figure 1. In the safety population, previous step I therapy was recorded in 29 patients (19%), whereas 122 patients (78%) were receiving WHO step II analgesic therapy prior to study entry. Other demographic data and patient clinical characteristics are reported in Tables 1 and 2. The initial NRM dosage was 5 mg every 4 h in 45 patients (29%) and 10 mg every 4 h in 111 patients (71%).

One patient treated with step I analgesic drugs and 15 patients treated with step II analgesics were treated with 10 mg NRM and 5 mg NRM every 4 h, respectively, considering the intermittent (only on demand) use of previous analgesic treatment.

With regard to the missing data for the primary outcome, the examination of the percentage of diary evaluations filled in out the number of evaluations expected (25 as a result of five pain evaluations a day for 5 days) shows an average compliance rate of 85%.

The mean percentage of the follow-up period with pain control in the ITT population was estimated to be 75% (95% CI 70–80). The same analysis conducted on the PP population showed very similar results: the mean proportion of the follow-up period with pain control was estimated to be 76% (95% CI 71–80), which is a further indication that it is unlikely that patients with very few observations (those included in the ITT, but not in the PP analysis) bias the results.

Figure 2 describes the distribution of the primary endpoint in the ITT population, which indicates that a very high percentage of patients (45%) achieved pain control for more than 90% of the follow-up period vs. only 7% who never reached it. Figure 3 shows the Kaplan–Meier failure function, which shows the cumulative percentage of patients who achieved pain control at each of the failure time-points. It can be observed that 24 h after the first oral NRM dose, pain control was achieved in 79% (95% CI 72–85) of the ITT population patients, with 50% of patients reaching pain control within the first 8 h. The median time needed to achieve pain control was 8 h (95% CI 4–8).

The mean pain score was 7.63 points at baseline, and decreased to 2.43 and 1.67 points (both $P < 0.001$) after 3 and 5 days of treatment respectively (Figure 4). The average NRM daily total dose in the first 5 days of follow-up was 59 mg (SD 33.6).

The most commonly reported adverse events and their mean intensity were: somnolence (24% of patients; mean intensity 1.49 ± SD 0.65), constipation (22%; mean intensity 1.68 ± 0.64), vomiting (13%; mean intensity 1.7 ± 0.57), nausea (10%; mean intensity 1.6 ± 1.63) and confusion (7%; mean intensity 1.36 ± 0.50). Adverse events occurred primarily in the first days of treatment, and with the exception of constipation, resolved without the need for further treatment. No unexpected adverse events were

Table 1 Demographic data and clinical characteristics of the patients

	Freq./	%
Sex		
Male	102	65.38
Female	54	34.62
Age (years)		
Mean (SD)	64.9 (10.7)	Range 29–87
Race		
Caucasian	156	100.00
Primary tumour		
Lung	35	22.44
Breast	18	11.54
Gastro-intestinal	34	21.79
Pancreas	9	5.77
Prostate	11	7.05
Kidney	7	4.49
Ovary	3	1.92
Skeletal	1	0.64
Connective tissue	1	0.64
Head-neck	8	5.13
Other	29	18.59
Presence of metastases		
Yes	135	86.54
No	21	13.46
Liver metastases		
Yes	36	23.08
No	120	76.92
Lung metastases		
Yes	30	19.23
No	126	80.77
Skeletal metastases		
Yes	70	44.87
No	86	55.13
CNS metastases		
Yes	4	2.56
No	152	97.44
Lymphonodal metastases		
Yes	41	26.28
No	115	73.72
Other metastases		
Yes	32	20.51
No	124	79.49
Mini mental state examination score		
7	6	3.85
8	8	5.13
9	36	23.08
10	106	67.95
Karnofsky performance status score		
30	4	2.52
40	14	8.81
50	5	3.14
60	24	15.09
70	38	23.90
80	45	28.30
90	14	8.81
100	15	9.43

Table 2 Baseline pain characteristics, analgesic drug intake and dose of NRM prescribed

	Freq./	%
Nociceptive pain		
Yes	132	84.6
No	24	15.38
Neuropathic pain		
Yes	55	35.26
No	101	64.74
Mixed pain		
Yes	75	48.08
No	81	51.92
Episodic pain		
Yes	85	54.49
No	71	45.51
Baseline analgesic drug intake		
No analgesic therapy	2	1.28
Step I	29	18.59
Step II	122	78.21
Missing data	3	1.92
NSAIDs/paracetamol* assumption		
Yes	102	65.38
No	54	34.62
Morphine prescribed daily dosage		
5 mg/4 h	45	28.85
10 mg/4 h	111	71.15

*NSAIDs, non-steroidal anti-inflammatory drug or paracetamol (step I of the WHO analgesic ladder) administered alone or in association with opioids.

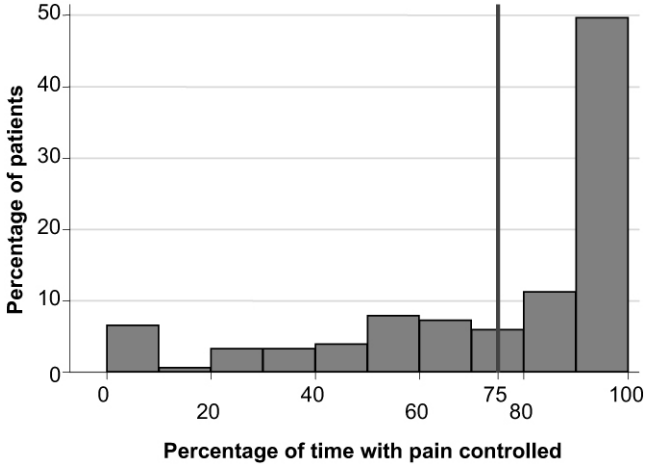

Figure 2 Distribution of the primary endpoint among trial participants. The red line indicates the mean proportion of time spent during the first 5 days of NRM treatment with pain control.

observed; four patients (3%) died during the study, but none of the deaths were related to the study drug.

Discussion

In this open-label study, oral NRM given initially at a dosage of 5 or 10 mg every 4 h, and uptitrated according to response, was able to control pain for 75% of the time during the first 5 days of treatment in patients with advanced cancer suffering from moderate-to-severe cancer pain. Pain control was achieved very quickly with 79% of patients experiencing pain control within the first 24 h of treatment; the median time to pain control was 8 h.

Titration is a pharmacological approach that allows a personalized analgesic treatment to be tailored to patient needs, mainly at the beginning of the treatment with

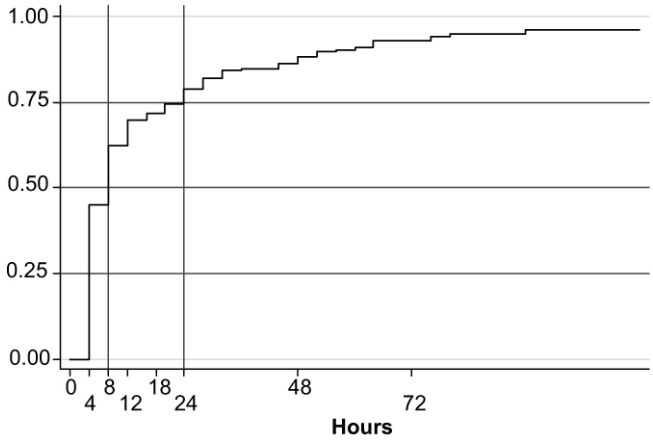

Figure 3 Kaplan–Meier failure function indicating the cumulative percentage of patients who achieved pain control at each of the failure time-points

strong opioids in patients with moderate-to-severe pain, through a close evaluation and re-evaluation of pain intensity and frequency as well as a careful evaluation of the effect and tolerability of the prescribed therapy. Immediate-release opioids are the ideal and most appropriate therapy during the titration phase because of their pharmacokinetics;[19–21] they allow 'real time' modifications of analgesic therapy, thus identifying in a short period of time the dose required for pain control or stable dose. After this phase, it is possible to consider other opioid analgesics as well as other administration routes,[3,22] and slow- or controlled release formulations, which are associated with better patient compliance rates.

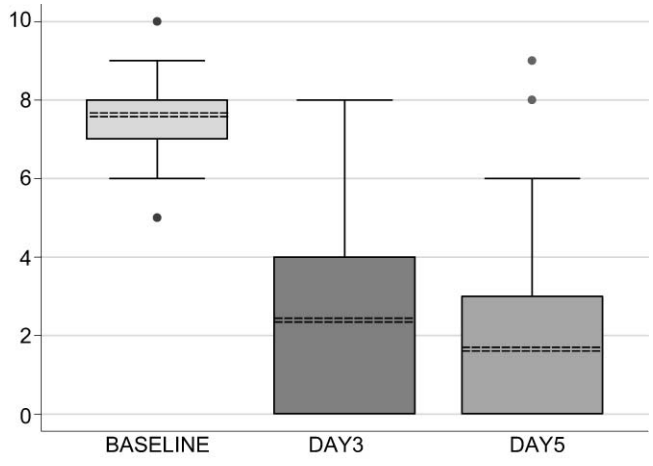

Figure 4 Mean pain scores observed at baseline and on days 3 and 5. *Box plots are graphs showing the distribution of a set of data through a box, which represents the middle 50% of the data, two 'whiskers' shown above and below the boxes are the lowest and highest values observed, and dots which indicate scores considering to be outliers

Despite European guidelines recommending pharmacological titration with NRM for patients with moderate-to-severe pain,[2,3,5,7] this therapeutic approach is poorly adhered to clinical practice.[16] In particular, there is a tendency in Italy to use controlled release opioid formulations or, even more frequently, transdermal systems[16] to start opioid therapy for moderate-to-severe cancer pain, thus avoiding the titration phase despite contraindications by United States Food and Drug Administration.[17]

We observed typical adverse events associated with opioids. These occurred mostly in the first days of therapy and tended to resolve spontaneously (with the exception of constipation) without the need for additional therapy.

The high frequency of episodic pain at baseline, before starting the NRM administration (55%) is to be considered a real and almost unavoidable possibility during the titration phase, when the tailored dose for each patient is being defined. It should be noted that this frequency is lower than that reported elsewhere (59–95%), where episodic pain is assessed in patients already under stable opioid treatment.[23–32]

This open-label study was carried out in 159 patients, a population which represents a large sample for NRM use, even though the population size was lower than originally planned. Furthermore, because the estimate of the primary outcome obtained was higher than assumed in the protocol (75% vs. 60%), the precision of the estimate remained at 10% as initially stated. The fact that the primary outcome was almost the same in the ITT and PP populations (75% vs. 76%) suggests that the missing data did not bias the results.

This trial confirms that NRM should be initiated as soon as possible in cancer patients with moderate-to-severe pain instead of starting therapy when the patient is at an advanced and terminal stage, as unfortunately is common in clinical practice. This opiophobia[33], in particular 'morphinophobia', leads physicians to use WHO step II drugs, such as codeine and tramadol[13] or transdermal systems,[15–17] for a long time.

We found an average compliance rate of 85%, which is very high for such a strict self-assessment instrument in a oncology/palliative care population. This compliance level also indicates that it is unlikely that missing data biased the results of an 'available data analysis' approach.

Conclusions

The results of the MERITO study indicate that oral NRM, administered according to the international EAPC Recommendations, can effectively and rapidly improve pain intensity, give sustained analgesia and an acceptable safety profile in strong-opioid-naïve patients

with moderate-to-severe cancer pain during the pharmacological titration phase when the dose of the opioid can be changed repeatedly over the same day to reach 'tailored analgesic therapy'.

This study was conducted in 16 palliative care units in Italy and it would be important to try and repeat this work in a more generalist setting where the majority of such patients are actually cared for.

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