A systematic review of the influence of opioids on advanced cancer patient survival

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A systematic review of the influence of opioids on advanced cancer patient survival

José Mario López-Saca\textsuperscript{a,b}, José López Guzmán\textsuperscript{c}, and Carlos Centeno\textsuperscript{a,b}

\textbf{Purpose of review}  
Many health professionals still believe that opioids shorten the lifespan of patients. This situation implies that the ethical doctrine of double effect is often invoked to justify their use in extreme circumstances. The objective of this study is to revise the evidence existing in the recently published literature regarding the effect on patient survival of opioid used to control disease symptoms.

\textbf{Recent findings}  
A review of the scientific literature regarding the effects of opioids on symptom control and survival does not provide any evidence that there is an association between these two variables.

\textbf{Summary}  
The studies revised have not shown that the use of opioids for symptom control in advanced disease stages or in the last days of life has any effect on patient survival. Similarly, survival was not influenced by either the use of higher or lower doses of opioids, or by the practice of administering a double dose at night.

\textbf{Keywords}  
morphine, opioids, palliative care, survival

\section*{INTRODUCTION}

Patients in palliative care present 4–10 symptoms a day on average, among which pain prevalence is between 70 and 80%, and dyspnoea 31\%\textsuperscript{[1]} The availability of drugs to alleviate these symptoms contributes to patient comfort and the family’s peace of mind. Nevertheless, health professionals have expressed reservations regarding the use of opioids, which may lead to their inadequate and insufficient use \textsuperscript{[2]}. An article published in 2005 highlighted the role of morphine and other opioids in the treatment of cancer-related pain, although it mentions that ‘morphine has been feared for a long time by the general public and the medical profession’ \textsuperscript{[3]}.

Morphine is recommended by the WHO for the first-line control of moderate to severe oncological pain and it is also used to manage dyspnoea, although at lower doses than those used for analgesia. Like any drug, it has secondary effects, many of which are well known and of which respiratory depression causes the greatest concern. In this sense, it must be born in mind that patients in advance disease stages may be more sensitive to drugs due to their deterioration or the elderly condition \textsuperscript{[4]}. In the medical world, it is considered that terminally ill patients have a right to receive ‘relief treatment for pain and suffering even when this management might shorten the patient’s life’ \textsuperscript{[5]}. This statement is supported by the doctrine of double effect (DDE) \textsuperscript{[6,7]}, first proposed in the XIII century by Saint Thomas Aquinas in the context of legitimate defence.

\section*{BASIC COMPONENTS OF THE DOUBLE EFFECT PRINCIPLE}

The basic components of the double effect principle are listed as follows:

(1) The action must be either morally good or indifferent (nature-of-the-act condition).

(2) The bad effect must not be the means by which one achieves the good effect (means-end condition).

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When a patient is admitted to a palliative care unit, he/she presents a mean of 4–10 different symptoms. In these patients, pain prevalence is between 70 and 80%, and dyspnoea 31%, although the latter increases up to 85% in last days. Having drugs available to alleviate these symptoms enhances the patient’s comfort and the family’s peace of mind.

Opioids drugs are effective in controlling these symptoms, although there are doubts regarding their safety for terminally ill patients, which results in undertreatment of pain and dyspnoea.

Some physician’s invoke the doctrine of double effect (DDE) in order to use opioids to treat patients at the end of their life.

A revision of the literature indicates that sensible opioid use at the end of a patient’s life does not hasten death. In the light of these results, there is ethically no need to invoke the DDE to justify their use.

The good effect must be at least equivalent in importance to the bad effect (proportionality condition).

The intention must be to achieve only the good effect, with the bad effect only being an unintended side effect (right intention condition).

The objective of this literature review is to evaluate the evidence in the recently published literature on the influence of opioids used for symptom control on survival of advanced cancer patients. The need to invoke the DDE to justify the use of opioids in symptom control in terminal patients is also addressed.

A literature review was carried out on studies in which the objective was to assess the effect of opioids used to provide relief for pain and dyspnoea on the survival of terminally ill patients.

Studies were included from the entire evidence pyramid: meta-analysis, systematic revisions, controlled clinical trials, cohorts and case series. The search was performed in MEDLINE, Trip Database and the Cochrane Library, and the ‘snowballing technique’ was used to identify more studies in the bibliographic references from the main articles.

The search strategy was sequential (Fig. 1), whereby:

In an initial electronic search, cohort studies were identified that best answered the research question. Two cohorts were found, a retrospective and a multicentre prospective cohort.

The search was then extended to other studies, identifying an additional 30 studies, of which 10 studies actually fulfilled the objectives established.

MeSH terms used in the electronic search


MORPHINE USE AND SURVIVAL

The starting point for this work was a review published in Lancet in 2003 [8] that focused on the use of opioids and sedatives at the end of life. Of the studies included in this review, five of them analysed the effect of opioids on survival by different approaches. We included four of the five articles in our revision, as we had to exclude one of the studies because it only marginally covered our research goal [9]. However, we complemented the review by Sykes by extending the number of articles to 10 (Table 1) [10–19].

None of the first four studies reported that opioids shortened the lifespan of patients. In the first study [10], patients receiving a double dose of opiates during the night were compared with those receiving lower doses. These authors concluded that patients receiving a double dose did not have a higher probability of dying during the night. Similarly, no detriment to survival was observed between patients that received high or low doses of morphine, but rather patients receiving high doses of morphine (300–599 mg/day) presented a higher mean survival than those receiving low doses [11]. This finding was corroborated in a more recent study of the survival of patients receiving different doses of opioids [12].

Studies comparing sustained opioids dosage may produce false results, and perhaps, the most important fact to assess survival following opioids administration should be the increase or change in doses. In this context, differences in survival were not observed in association with increasing rates of the opiate administration [13], and in this study,
large increases in dose in these patients were not evident before the last 48 h of life.

The data published in six recent studies are also consistent with the original *Lancet* review, involving a larger number of patients and including other variables such as diagnosis, age, functional capacity and so on. In a retrospective study of 435 patients in their homes, one of the conclusions drawn was that the survival of patients who received high and very high doses of morphine (300–599 and ≥600 mg/day, respectively) was longer than in those who received low doses ($P = 0.001$) [14]. A similar retrospective study [15] of 229 clinical histories from a palliative care unit carried out a year later also aimed to establish the relationship between opioids use and the survival of patients with terminal cancer. In this cohort, the use of high morphine doses was not associated with a significant increase in the days of hospitalization.

In 2006, a cohort of 725 patients admitted to 13 hospices in the USA was followed to determine whether high and very high doses of opioids affected survival [16]. The mean survival of this population was $12.46 \pm 23.11$ days between the last change in opioids and death. However, when the patients were divided into subgroups depending on the doses of opioids received, those who received higher doses, equivalent to oral morphine of 1800 mg/day, survived longer than those who received doses below 600 mg/day ($P = 0.0042$).

Indeed, a multivariate analysis showed a significant association between short survival, higher opiate doses, cancer diagnosis and the degree of altered consciousness and pain less than 5 in a numeric scale of 0–10. This analysis revealed that among other factors, the final opioid dose was associated significantly with a shorter survival time, although this association was very weak and only accounts for a small percentage of the variance in survival (5–7%). It was concluded that in a population of terminally ill patients, survival depends on a complex series of factors, many of which cannot be measured. Nevertheless, but fear of accelerating death does not justify not using opiates in these patients.

Four years later, a cohort of 223 patients admitted to a hospital in Vizcaya (Spain), and who were subsequently followed-up in their homes, was studied [17]. This cohort was made up of terminally ill patients older than 18 years, and it considered demographic and clinical variables, including ECOG-PS (Eastern Cooperative Oncology Group,
Table 1. Studies about the use of opiates and their influence on the survival of oncological patients 1987–2012

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study objectives</th>
<th>N</th>
<th>Study type</th>
<th>Patient location</th>
<th>Groups studied and opiate dosea</th>
<th>Survival</th>
<th>Statistical test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regnard and Badger [10]</td>
<td>To compare the last day of life of patients receiving a double opioids dose at night with those receiving a single dose</td>
<td>137</td>
<td>Retrospective from notes in clinical histories</td>
<td>Admitted to general hospital</td>
<td>Group A: Single dose at night 22:00h (n = 87)</td>
<td>No significant differences between A and B were observed: 41% died overnight in A and 32% in B</td>
<td>x²</td>
<td>0.28</td>
</tr>
<tr>
<td>Bercovitch et al. [11]</td>
<td>To verify whether the use of high morphine doses affects patient survival</td>
<td>453</td>
<td>Retrospective. To compare patients treated with &gt;300 mg/day morphine with the other patients treated</td>
<td>Admitted to hospice</td>
<td>Group A: &lt;300 mg (n = 398)</td>
<td>No significant differences between A and B were observed: 14 vs. 15 days</td>
<td>Kaplan–Meier survival curve</td>
<td>Not included</td>
</tr>
<tr>
<td>Thoms and Sykes [13]</td>
<td>To assess whether the use of opioids for symptom control is associated with life shortening</td>
<td>238</td>
<td>Retrospective</td>
<td>Patients in their last week of life admitted to a palliative care unit</td>
<td>Group A: &gt;50% doses in last 48 h (n = 28)</td>
<td>No significant differences were observed between A and B: 9 vs. 3 days</td>
<td>Test</td>
<td>0.7</td>
</tr>
<tr>
<td>Morita et al. [12]</td>
<td>To examine the effect on survival of the use of opioids and sedatives in the last 48 h</td>
<td>172</td>
<td>Prospective observational</td>
<td>Admitted to a palliative care unit</td>
<td>Group A: 240 mg (n = 114)</td>
<td>No significant differences were observed between A, B and C</td>
<td>Univariate analysis</td>
<td>0.23</td>
</tr>
<tr>
<td>Bercovitch and Adunsky [14]</td>
<td>To evaluate the effect of the use of high morphine doses on survival</td>
<td>435</td>
<td>Retrospective. Compares patients administered different ranges of doses</td>
<td>Patients in their homes with palliative care</td>
<td>Group A: 5–299 mg/day (n = 396)</td>
<td>Higher survival is observed with higher doses A, B and C: 22 vs. 27 vs. 37 days</td>
<td>Mantel–Cox and Breslow analysis</td>
<td>0.001</td>
</tr>
<tr>
<td>Good et al. [15]</td>
<td>To evaluate the effect of opioids and sedatives in palliative patient survival</td>
<td>229</td>
<td>Retrospective. Comparing patients on different doses from their admission to their death</td>
<td>Patients admitted to a palliative care unit</td>
<td>Group A: &lt;120 mg/day</td>
<td>The higher the dose, the longer the survival is observed in A, B and C: 11 vs. 13 vs. 18 days</td>
<td>Log-rank test</td>
<td>0.01</td>
</tr>
<tr>
<td>Portenoy et al. [16]</td>
<td>To determine whether high and very high opioids doses affect survival</td>
<td>725</td>
<td>Cohort, prospective multicentre</td>
<td>Patients admitted to 13 different hospices in the USA</td>
<td>A1: &lt;600 mg/day (n = 640)</td>
<td>The final opioid dose was one of the significant factors associated with shorter survival, although it only explains 6% of the variance.</td>
<td>Multivariate analysis with least square regression</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Comparing the mean length of stay of patients treated with different doses of morphine (normal) doses vs. high doses: cut-off point 600 mg; and not very high doses vs. very high doses, cut-off point 1800 mg

<table>
<thead>
<tr>
<th>A2: &gt;600 mg/day (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1: &lt;1800 mg/day (n = 706)</td>
</tr>
<tr>
<td>B2: &gt;1800 mg/day. (n = 19)</td>
</tr>
</tbody>
</table>

Bengoechea et al. [17] To determine whether the total opioids dose and the increase in dose during the last days affects survival 223 Retrospective cohort. Comparing patient subgroups with different doses of opioids and whether or not they duplicated the previous dose in the studied period Terminal cancer patients in their homes receiving palliative care A1: <120 mg/day (n = 124) A1: 2 days. Log-rank test 0.010

<table>
<thead>
<tr>
<th>A2: &gt;120 mg/day (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 vs. A2; B1 vs. B2 0.0001</td>
</tr>
</tbody>
</table>

B1: did not duplicate previous dose (n = 156) B1: 9 days. Multivariate analysis 0.0001

B2: duplicated previous dose (n = 67) B2: 22 days. Cox regression

Radha Krishna [18] To examine whether the use of opioids in cancer patients in their last days of life decreases survival 238 Retrospective observational study based on the notes in clinical histories Patients admitted to an oncology service to receive palliative care Group A: received opiates in the last 48 h (mean: 48 mg/day) No significant difference in survival between those that received opioids and those who did not Kaplan–Meier survival curve 0.69

<table>
<thead>
<tr>
<th>Group B: received opiates in the last 24 h (mean: 57 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C: did not receive opiates in the last 48 h</td>
</tr>
</tbody>
</table>

Group B: No changes in dose (n = 21) Aspects related to higher or increased doses did not significantly affect survival Cox proportional hazard model

Group C: decrease in dose (n = 20)

Azoulay et al. [19] To examine whether survival in a hospice is affected by the use of opioids 114 Retrospective in consecutive patients Patients admitted to a hospice Dose: 146 ± 245 mg/day The survival in Group A was longer than Groups B and C Kaplan–Meier survival curve 0.01

<table>
<thead>
<tr>
<th>Group A: increase dose (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean survival: 12.3 ± 12.5 days</td>
</tr>
</tbody>
</table>

Group B: no changes in dose (n = 21) Aspects related to higher or increased doses did not significantly affect survival

Group C: decrease in dose (n = 20)

Other aspects related to the opioids dose: (1) initial dose; (2) dose at the time of death; (3) mean dose; (4) absolute variation; (5) daily increase

©OME, oral morphine equivalent.

*Mean survival data were not reported in this study. An approximate value has been extrapolated from the published survival graph.

*Patients survived a mean of 12 days (±2.3) from the last change in opioid dose.

*Multivariate analysis shows that among other variables, there is a significant association between longer survival and the previous doubling of the dose. The age and ECOG 4 were other variables that were significantly related.
Performance Status Scale); opiate dose, type of cancer and coadjuvant analgesic medication. The authors found that the mean survival was longer in patients who received higher opioids doses (6 days) than in those who received low doses (2 days; $P=0.010$). These differences disappeared once the variables were adjusted ($P=0.338$), as occurred in the earlier study. Moreover, the patients who received more than double the initial dose also survived for longer (22 days) than those who did not receive any change of dose (9 days; $P=0.0001$), differences that were also evident after the multivariate analysis ($P<0.0001$).

In the same year, a retrospective study [18] was published from clinical histories of 238 patients who received palliative care on admission to an oncology unit. In addition to describing different parameters of opioids use, this study also compared those individuals who received opioids in the last 48 h of life with patients who did not receive them using a Kaplan–Meier curve, observing no significant difference between these two groups ($P=0.69$). The last retrospective study published in 2011 [19] compared three variables: increasing the dose, keeping the same dose and decreasing the dose. Survival was not seen to diminish in patients who received increasing doses of opioids ($P=0.01$).

**DISCUSSION**

We have reviewed 10 articles published in the last 25 years that have assessed the use of opioids in patients at advanced or terminal stages of illness. The fear of using opioids at the end of life is a global problem, as reflected by the diverse countries from which the scientific articles originate (UK, USA, Japan, Israel, Singapore, Spain and Australia).

The first studies are retrospective and they compared patient’s receiving different doses of opioids in the last days of their life, finding no differences between the doses administered and a shortening of life. From 2004, until the last study published in 2011, and including two cohort studies, dose increases, the use of double doses and very high opiate doses were seen not to decrease survival. Perhaps paradoxically, in all these studies, higher opiate doses were associated with longer high survival, which we believe may be due to the relief provided by morphine. In one of the cohorts, a multivariate analysis indicated that the final opiate dose is one of the factors associated with lower survival, although it only accounted for 6% of the variance, with the remainder related to other variables such as cancer diagnosis, deterioration of the cognitive state and pain intensity less than 5 in a Verbal Numeric Scale from 0 to 10.

The use of opioids to control symptoms in the terminally ill is well tolerated and effective. The most frequent secondary effects reported in the studies were constipation, nausea and sleepiness. Research into the working protocols at hospices demonstrated that administration of opioids drugs at fixed intervals (e.g. a normal dose at a fixed time) is more effective to achieve pain relief than administering them on demand [20]. A study [21] into medical care at hospices described how the use of high morphine doses in terminally ill patients has a high clinical safety profile, concluding that morphine does not negatively affect the patient’s survival. Although some studies may have certain methodological deficiencies, we do not believe that any more studies are needed to confirm these data.

**DOCTRINE OF DOUBLE EFFECT**

In 1957, during the trial for the death of an elderly woman, Dr Bodkin Adams was accused of accelerating her death while trying to alleviate pain with morphine [22]. In a similar case in 1999, Dr David Moor used diamorphine to alleviate the pain of an 85-year-old man suffering from colon cancer and who was in agony. His lawyer appealed to the DDE, and he was acquitted of the accusation of having shortened the life of the patient [23]. The DDE states that ‘the potential and undesired risk, as a consequence of a treatment, is justified if the purpose and intention of the treatment benefits the patient, the situation must be serious to accept the risk and the wish to benefit must always prevail’ (Fig. 1) [24].

There is a fear among clinicians of shortening the life of patients by using morphine in a terminal situation, and in such cases, the DDE may be invoked to justify its use. However all the available studies show that the use of opiates does not shorten the patient’s life, and therefore, it is not necessary to invoke the DDE in order to use opioids. By contrast, what is not ethical is ‘opium-phobia’.

**CONCLUSION**

Since the 1980s, morphine has been used to achieve symptom relief in terminally ill patients and there is no evidence that this accelerates death. In the studies that have been performed, we do not observe statistically significant differences in patient survival with the higher opioids doses used, or with an increase in the doses administered in the last days of life. Similarly, the practice of applying a double dose at night does not represent a risk for survival. Given these data, it is not necessary to invoke the DDE in order to justify the use of opioids for symptom relief at the end of life.
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Conflicts of interest
The authors have not declared any conflicts of interest.

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