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Transdermal opioids as front line treatment of moderate to severe cancer pain: a systemic review

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Abstract

Background: To assess the role of transdermal opioids as a front-line approach to moderate to severe cancer pain.

Methods: A systematic review of the literature was performed by two authors. An analysis of the level of evidence and risk/benefit ratio was performed for all of the selected trials. A combined analysis of the included studies to assess the level of evidence, risk/benefit ratio and strength of the recommendations was performed to determine the place of transdermal opioids in the treatment of cancer when compared with oral morphine.

Results: Thirteen papers were included in the analysis. The level of evidence was considered low for transdermal opioids (without distinction between transdermal fentanyl and transdermal buprenorphine) or transdermal fentanyl, and very low for transdermal buprenorphine. The risk/benefit ratio was considered uncertain for both transdermal opioids (fentanyl and buprenorphine) considered together and transdermal fentanyl or buprenorphine alone. The strength of the final recommendations (using the GRADE system) was weak negative for transdermal opioids (transdermal fentanyl plus transdermal buprenorphine) and transdermal fentanyl, and strong negative for transdermal buprenorphine.

Conclusions: The use of slow release oral morphine probably remains the preferred approach for these patients, with the use of transdermal opioids to be reserved for selected patients.

Keywords
Neoplasm, pain, opioids, administration, cutaneous

Introduction

Oral morphine represents the treatment of choice for moderate to severe cancer pain, and most scientific societies recommend its use as the first-line approach in patients moving from the second to the third step of the analgesic ladder.1–4 Likewise, transdermal opioids (and particularly transdermal fentanyl) are recommended for those patients in whom the oral route is not suitable or in whom oral morphine is ineffective or associated with intractable side effects.3,5

Nevertheless, in spite of the recommendations of scientific societies, the use of transdermal opioids (mainly transdermal fentanyl) in recent years has increased substantially as a first-line approach to moderate to severe cancer pain. The reasons for this increase in use by physicians (mainly oncologists and general practitioners) are various and only partly reported in the literature.6,7 Amongst the reasons given to support the extensive use of transdermal opioids in front-line moderate to severe cancer pain include a better compliance of the patient, better safety profile and the preference of the patient. On the other hand, the reasons for not choosing them include a lack of evidence supporting the superiority of transdermal opioids when compared with oral morphine, the risk of severe side effects, the
negative influence of marketing pressure on most oncologists or general practitioners and higher costs of the treatment in comparison with oral opioids.\textsuperscript{6–10}

Two considerations need to be made as a preliminary approach to the problem:

although oral morphine (in immediate and slow release formulations) represents the opioid of first choice for the relief of moderate to severe cancer pain, the evidence supporting its use is modest, and of low power from a methodological, evidence-based point of view;\textsuperscript{11,12}

although the data can be considered inconclusive, some trials comparing the efficacy and safety of transdermal opioids with oral morphine and placebo exist in the literature, and could be even sufficient to justify a slightly less rigorous adherence to standard treatment with oral morphine.\textsuperscript{13,14}

In recent years, we have examined the role of transdermal opioids in the treatment of cancer pain, and the two meta-analyses we recently published report the evidence demonstrating mainly the differences in the safety profiles of transdermal opioids or oral morphine.\textsuperscript{13,14} In this paper, we review once more the actual evidence supporting a hypothetical use of transdermal opioids in front-line moderate to severe cancer pain, classifying all the evidence and producing final recommendations using the GRADE system.\textsuperscript{15–21} This new study, which is obviously strictly related with the data of our previous meta-analyses,\textsuperscript{13,14} has the novel, ambitious aim of overcoming the dimension of clinical research (proper of phase III randomized clinical trials or meta-analyses) to reach and guide the daily practice with practical, ‘evidence-based’ clinical recommendations.

**Methods**

**Questions and targets**

The clinical problem to be solved is ‘What is the evidence showing that transdermal opioids are better than placebo or other opioids in the management of pain in adult patients with moderate to severe cancer pain, never treated with strong opioids and requiring stable doses of opioids?’ It follows that the target of our research are adult patients with cancer pain, requiring stable doses of strong opioids, never treated with strong opioids for chronic pain. We have analysed the efficacy and safety of two strategies of treatment using transdermal opioids (buprenorphine and fentanyl) in comparison with oral morphine, which according to most literature guidelines is the first-choice opioid for patients with moderate to severe cancer pain.\textsuperscript{1–4} The final outcomes of our search were the efficacy and safety of transdermal opioids (buprenorphine or fentanyl) when compared with oral morphine in the treatment of moderate to severe cancer pain; the analgesic effect was the primary outcome of our search and the safety or patient’s preferences were the secondary ones. The main questions and the P.I.C.O. (Population, Intervention, Comparison, Outcome) of our search are detailed in Table 1.

**Search strategy**

A systematic review of MEDLINE, EMBASE, CINAHL, CRISP and Cochrane Systematic Reviews Databases, from January 1966 to December 2009, was independently performed by two authors (DT and MM), using \{\{Fentanyl\} or Buprenorphine\} and Pain\} or Neoplasm\} or \{Fentanyl\} or Buprenorphine\} and Palliative Care\}, or \{Administration, Cutaneous\} and Opioids\} and Pain\} or Neoplasm\}. A pooled analysis included trials testing both transdermal buprenorphine and transdermal fentanyl, and two separate analyses of transdermal buprenorphine and transdermal fentanyl were performed to answer the question about using either transdermal opioid (tou court) or buprenorphine or fentanyl. All randomized phase III trials comparing transdermal fentanyl or transdermal buprenorphine with placebo, oral morphine or other strong opioids were considered eligible for the analysis. Whenever no randomized phase III trials were retrieved in the primary search, all phase II trials or patients’ series were considered eligible and included in the analysis. Whenever one or more than one randomized phase III trial were retrieved in the primary search, all phase II trials or case series were excluded from the analysis if they did not add any further information to the phase III trials data. All references of the retrieved trials and all systematic reviews published from January 1966 to December 2009 were analysed, and all retrieved trials for analysis were included if eligible. When discrepancies in trials searching occurred between the two independent reviewers (DT and MM), they were discussed with a third researcher (MR) to reach a final consensus.

**Analysis of the evidence and definition of the strength of the recommendations**

All data from the eligible trials were analysed using the GRADE system, to define the quality of the evidence and to determine the strength of the recommendations for clinical practice.\textsuperscript{15–21} According to the GRADE approach, a three-step analysis was performed for all
Table 1. Clinical questions and P.I.C.O. (Population, Intervention, Comparison, Outcome) of the review

| Question 1. | In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that transdermal opioids are better than placebo, or other oral opioids in the management of pain? |
| Population | Patients with moderate severe cancer pain who need strong opioids, and that are opioid naive or failed treatment with weak opioids in the second step of the analgesic ladder. In all the patients the opioid needs had to be stable and defined with adequate opioid titration. |
| Intervention | Treatment with transdermal opioids. |
| Comparison | Slow release oral morphine. |
| Outcome | Analgesic effect (primary outcome); Safety (secondary outcome); Patient’s preferences (secondary outcome). |

| Question 2. | In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that transdermal fentanyl is better than placebo, or other oral/transdermal opioids in the management of pain? |
| Population | Patients with moderate severe cancer pain who need strong opioids, and that are opioid naive or failed a treatment with weak opioids in the second step of the analgesic ladder. In all the patients the opioid needs had to be stable and defined with adequate opioid titration. |
| Intervention | Treatment with transdermal fentanyl. |
| Comparison | Slow release oral morphine. |
| Outcome | Analgesic effect (primary outcome); Safety (secondary outcome); Patient’s preferences (secondary outcome). |

| Question 3. | In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that transdermal buprenorphine is better than placebo, or other oral/transdermal opioids in the management of pain? |
| Population | Patients with moderate severe cancer pain who need strong opioids, and that are opioid naive or failed a treatment with weak opioids in the second step of the analgesic ladder. In all the patients the opioid needs had to be stable and defined with adequate opioid titration. |
| Intervention | Treatment with transdermal buprenorphine. |
| Comparison | Slow release oral morphine. |
| Outcome | Analgesic effect (primary outcome); Safety (secondary outcome); Patient’s preferences (secondary outcome). |

data extracted from the literature review, to define respectively the quality of the evidence, the risk/benefit ratio and the strength of the final recommendations (Figure 1). The quality of the evidence and the risk/benefit ratio were both assessed in all the trials identified as eligible by two researchers (DT and MR) and in the comprehensive analysis of all the selected trials about the topic. The strength of the recommendations was assessed uniquely for the final response to the clinically significant questions by the same two researchers. The results of the analysis were discussed by all the authors in an analysis according to the preliminary report by DT and MR, and a statement about the level of evidence, the risk/benefit ratio and the strength of the recommendations was finally produced to guide clinical practice. The strength of the recommendations was reported both for the use of transdermal opioids (transdermal fentanyl or transdermal buprenorphine) and for the use specifically of transdermal fentanyl or transdermal buprenorphine, respectively.
Results
Systematic review of the literature
Four hundred and thirty-four papers were found using the first string ({"Fentanyl"[Mesh] or "Buprenorphine"[Mesh] and “Pain”[Mesh] and “Neoplasm”[Mesh]}), and 136 of these were considered potentially eligible for the final analysis. One hundred and twenty-eight papers were found using the second string ({"Fentanyl"[Mesh] or "Buprenorphine"[Mesh] and “Palliative Care”[Mesh]}), and 31 of these were considered potentially eligible for the final analysis. Eighty papers were found using the third string ({"Administration, Cutaneous”[Mesh] and “Opioids”} and “Pain”[Mesh] and “Neoplasm”[Mesh]}), and 35 of these were considered potentially eligible for the final analysis. Finally, 13 papers were considered eligible and included in the analysis: two of these papers report data of two different meta-analyses investigating the role of transdermal opioids (buprenorphine and fentanyl) in cancer pain, three trials report data of randomized clinical trials comparing transdermal fentanyl with oral morphine in cancer pain, and one paper reports data of a randomized clinical trial comparing transdermal fentanyl with oral morphine and oral methadone, one trial reports data of a randomized clinical trial comparing transdermal fentanyl with subcutaneous morphine, one paper reports data of a randomized clinical trial comparing transdermal buprenorphine with oral morphine, three papers report data of randomized clinical trials comparing transdermal buprenorphine with placebo, and one paper reports data of a randomized trial comparing transdermal fentanyl with placebo. The main characteristics of the selected trials are reported in Table 2.

Analysis of the evidence and identification of the risk/benefit ratio
All the selected papers were considered suitable to answer the question about the role of transdermal opioids in the front-line approach to moderate to severe cancer pain; as two of the selected papers investigated the role of transdermal fentanyl and transdermal buprenorphine and were included in both the two sub-analyses, a total of nine papers were suitable to answer the question about the role of transdermal fentanyl in the front-line approach to moderate to severe cancer pain; and six papers were suitable to answer the question about the role of transdermal buprenorphine as a front-line approach to moderate to severe cancer pain. A comparison of transdermal opioids with placebo was reported in four papers (transdermal buprenorphine versus placebo...
in three papers, a comparison with oral morphine was reported in seven papers, a comparison with subcutaneous morphine was reported in one paper, a comparison with oral methadone in one paper, a comparison with oral hydromorphone in one paper and a head-to-head comparison (transdermal fentanyl versus transdermal buprenorphine) in one paper. Based on the GRADE approach, the level of evidence was considered low in four papers and very low in nine papers. The main reasons for the low level of the evidence extracted from randomized clinical trials or meta-analyses included low statistical power, methodological limits in trials design and conduction, use of surrogate end points in the efficacy and safety analysis, questionable use of placebo as the comparator in four trials and an unclear identification of the comparator in the more recent trials.

Table 2. Main characteristics of the selected papers

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statistical design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmedzai and Brooks (1997)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Slow release oral morphine</td>
<td>Pain control, quality of life, Safety</td>
</tr>
<tr>
<td>Hunt et al. (1999)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Subcutaneous morphine</td>
<td>Pain control</td>
</tr>
<tr>
<td>Mercadante et al. (2008)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Slow release oral morphine, oral methadone</td>
<td>Safety, cost</td>
</tr>
<tr>
<td>Pace et al. (2007)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal buprenorphine</td>
<td>Slow release oral morphine</td>
<td>Pain control, mental health, vitality, safety</td>
</tr>
<tr>
<td>Poulain et al. (2008)</td>
<td>Randomized clinical trial</td>
<td>Cancer patient</td>
<td>Transdermal buprenorphine</td>
<td>Placebo</td>
<td>Pain control</td>
</tr>
<tr>
<td>Kongsgaard and Poulain (1998)</td>
<td>Randomized clinical trial</td>
<td>Cancer patient</td>
<td>Transdermal fentanyl</td>
<td>Placebo</td>
<td>Pain control</td>
</tr>
<tr>
<td>Sittl et al. (2003)</td>
<td>Randomized clinical trial</td>
<td>Cancer and non-cancer patients</td>
<td>Transdermal buprenorphine</td>
<td>Placebo</td>
<td>Pain control, safety</td>
</tr>
<tr>
<td>Sorge and Sittel (2004)</td>
<td>Randomized clinical trial</td>
<td>Cancer and non-cancer patients</td>
<td>Transdermal buprenorphine</td>
<td>Placebo</td>
<td>Pain control, safety</td>
</tr>
<tr>
<td>Tassinari et al. (2008)</td>
<td>Meta-analysis of randomized clinical trials</td>
<td>Cancer patients</td>
<td>Transdermal opioids</td>
<td>Slow release oral morphine</td>
<td>Safety, patient’s preference</td>
</tr>
<tr>
<td>Tassinari et al. (2009)</td>
<td>Meta-analysis of randomized clinical trials</td>
<td>Cancer and non-cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Slow release oral morphine</td>
<td>Safety, patient’s preference</td>
</tr>
<tr>
<td>vanSeventer et al. (2003)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Slow release oral morphine</td>
<td>Pain control, safety</td>
</tr>
<tr>
<td>Wirtz et al. (2009)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal opioids</td>
<td>Slow release hydromorphone</td>
<td>Nausea, emesis, constipation</td>
</tr>
<tr>
<td>Wong et al. (1997)</td>
<td>Randomized clinical trial</td>
<td>Cancer patients</td>
<td>Transdermal fentanyl</td>
<td>Slow release oral morphine</td>
<td>Pain Control, Quality of Life</td>
</tr>
</tbody>
</table>
trials\textsuperscript{13,14,22–24,26,28}, no significant differences were found in the analgesic effect between the two strategies, and the main differences can be extracted in the safety profile and in the preferences of the patient (reported only for transdermal fentanyl). The size of safety and side effects of transdermal opioids in comparison with slow release oral morphine is shown in all the selected trials, and it is clearly detailed in the two meta-analysis performed by our group.\textsuperscript{13,14} Both the analyses seem to suggest a lower constipation rate in the patients treated with transdermal opioids when compared with oral morphine, supporting a significant preference of the patients for transdermal opioids instead of oral morphine (the datum can be extracted only from trials using transdermal fentanyl). Moreover, the paper reporting data about transdermal fentanyl in cancer and non-cancer patients revealed a significant lower incidence of constipation, urinary retention and laxative use in patients treated with transdermal fentanyl, and it also showed a significant lower incidence of diarrhea, nausea and sweating in patients treated with oral morphine.\textsuperscript{14} The use of heterogenic criteria for the assessment of the side effects between the trials, and the frequently equivocal reporting of side effects and quality of life, support a non-univocal definition of the risk/benefit in all the trials. Furthermore, the risk/benefit ratio needs to be defined as uncertain (or at least weakly favourable for transdermal fentanyl) both in the transdermal opioids group and in the transdermal buprenorphine or transdermal fentanyl groups. All the data about the quality of the evidence and the risk/benefit ratio are reported in Table 3.

**Final analysis of the quality of the evidence, risk/benefit ratio and strength of the recommendations**

The analysis of the evidence extracted from the selected papers and the identification of the risk/benefit ratio in the single trials lead to a final analysis to answer the three questions of the clinical practice. Overall, when the role of transdermal opioids in the front-line approach to moderate-severe cancer pain is investigated and compared with slow release oral morphine, the level of evidence supporting their front-line use is low, with an uncertain risk/benefit ratio (mainly based on the better safety profile) and an uncertain trade-off recommendation to their use in all the strong-opioid naive patients with moderate to severe cancer pain. Likewise, when we distinguish transdermal fentanyl from transdermal buprenorphine, the final considerations can reach similar conclusions. In detail, when we take into account the use of transdermal fentanyl in the front-line approach to moderate to severe cancer pain, the level of evidence can be considered low, with an uncertain risk/benefit ratio and an uncertain trade-off recommendation for their use in the clinical practice in all the strong-opioid naive patients with moderate to severe cancer pain, while when we take into account transdermal buprenorphine, the level of evidence can be considered very low, with an uncertain risk/benefit ratio and a no net benefit recommendation for their use as a front-line approach in all the patients of the clinical practice. Due to the minor relevance of the literature data and a questionable identification of the comparator in the trials reported in the selected papers, we were unable to extrapolate final considerations about the comparison of transdermal opioids with subcutaneous morphine, oral methadone or hydromorphone.

**Discussion**

Most clinical guidelines published by the main scientific societies are known to recommend oral morphine as the treatment of choice for patients with moderate to severe cancer pain, who need a treatment with a strong opioid and are strong-opioid naive.\textsuperscript{1–4} Likewise, it is well known that the World Health Organization (WHO) three-step ladder is the gold standard for the treatment of cancer pain, and that most patients with cancer pain can be treated only with a medical approach, avoiding any invasive procedure for the pain treatment.\textsuperscript{1,33–41} Nevertheless, one of the most controversial aspects of palliative care is the lack of strong evidence supporting its milestones, and both the use of oral morphine and the validation of the WHO analgesic ladder are lacking strong evidence of efficacy in the treatment of cancer pain.\textsuperscript{3,11,12} Despite the validation of the use of oral morphine, whose efficacy is quite modestly supported by adequately designed trials,\textsuperscript{33–41} the use of transdermal opioids has been largely investigated in recent years, and two published meta-analyses\textsuperscript{13,14} and an ongoing Cochrane review\textsuperscript{42} seem to demonstrate a more rigorous approach to the problem when compared with the supported oral morphine in moderate to severe cancer pain. Consequently, the first problem is the identification of oral morphine as the gold standard, and all the modern approaches that have been recently introduced in clinical practice should be compared with oral morphine to demonstrate their efficacy/safety. On the whole, the evidence supporting the use of oral morphine is based on case series or case reports, and in 2001 the European Association for Palliative Care classified all these evidence as level C in its recommendations. Transdermal opioids have been recently introduced in the clinical practice, and the evidence supporting their use is based on randomized clinical trials or meta-analyses, whose levels of evidence are undoubtedly greater than those supporting the use of oral morphine. These data deserve to be evaluated.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Level of Evidence</th>
<th>Factors Influencing the Final Level of the Evidence</th>
<th>Final Level of Evidence</th>
<th>Factors Influencing the Risk/Benefit Ratio</th>
<th>Risk/Benefit Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmedzai et al (1997)²²</td>
<td>High</td>
<td>High number of missing data. Use of surrogate end point. Use on non validated tool to assess the benefit. Sponsored trial.</td>
<td>Very Low</td>
<td>Use of surrogate end point. Use on non validated tool to assess the benefit.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Hunt et al (1999)²⁷</td>
<td>High</td>
<td>Unpowered design of the trial. Use on non validated tool to assess the benefit. Sponsored trial.</td>
<td>Very Low</td>
<td>Use on non validated tool to assess the benefit.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Mercadante et al (2008)²⁶</td>
<td>High</td>
<td>Unpowered design of the trial. Many biases in the conduction of the trial.</td>
<td>Very Low</td>
<td>Use of surrogate end point.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Pace et al (2007)²⁸</td>
<td>High</td>
<td>Unpowered design of the trial. Many biases in the conduction of the trial.</td>
<td>Very Low</td>
<td>Use of surrogate end point.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Kongsgaard et al (1998)³²</td>
<td>High</td>
<td>High number of missing data. Use of surrogate end point. Use on non validated tool to assess the benefit. Use of placebo as comparator. Unexpected high placebo response.</td>
<td>Very low</td>
<td>Use of placebo as comparator.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Tassinari et al (2008)¹³</td>
<td>High</td>
<td>Heterogeneity between the trial. Use of non validated tool to assess the benefit.</td>
<td>Low</td>
<td>Use of non validated tool to assess the benefit. Lack of data about the analgesic effect.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Tassinari et al (2009)¹⁴</td>
<td>High</td>
<td>Heterogeneity between the trial. Use of non validated tool to assess the benefit.</td>
<td>Low</td>
<td>Lack of data about the analgesic effect.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>vanSeventer et al (2003)²⁴</td>
<td>High</td>
<td>Minor relevance of the primary end point. Use of non validated tool to assess the benefit. Sponsored trial.</td>
<td>Low</td>
<td>Minor relevance of the primary end point. Use of non validated tool to assess the benefit. Minor data about the analgesic effect.</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Wong et al (1997)²¹</td>
<td>High</td>
<td>Unpowered design of the trial. Many biases in the conduction of the trial. Sponsored trial.</td>
<td>Very Low</td>
<td>Use of surrogate end point. Use on non validated tool to assess the benefit.</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

Legend: §: the primary level of evidence is based on the basis of the design of the trial (high for randomized clinical trials and very low for the case-series); the final level of the evidence is pondered on the basis of the factors than can influence improving or reducing the primary level of the evidence, according with the GRADE system.¹³⁻²¹
in detail. In our systematic review of the literature, we identified that the comparator in randomized clinical trials was placebo in four trials, oral morphine in seven trials, subcutaneous morphine in one trial, hydro- morphine in one trial and oral methadone in one trial. The choice of the comparator represents the first critical aspect of our analysis: if oral morphine is the actual gold standard in the front-line approach to moderate to severe cancer pain, every comparison with placebo should be considered at least questionable, while every comparison with different strong opioids are probably not supported by adequate evidence that could justify the design and the conduction of the trial (defined as a phase III randomized trial, and needing the gold standard as the comparator arm).

Therefore, if we consider only trials comparing transdermal opioids with oral morphine, the first aspect that needs to be analysed is the detection of the outcome of the trials; in all trials, a comparison of the analgesic effect has only a secondary value, and the occurrence of side effects (mainly gastrointestinal) is the main benefit identified to justify a superiority of transdermal opioids. Although in a well-designed randomized clinical trial comparing two opioids the use of the equianalgesic doses between the two arms can clearly mask the differences in the analgesic effect, focusing the attention only on a limited number of side effects can be restrictive in a comprehensive analysis of the risk/benefit ratio for both clinical research and clinical practice. This aspect is particularly evident in our review, where few of the selected trials demonstrated only a significant reduction of constipation in patients treated with transdermal opioids when compared with oral morphine. This finding is surely interesting from a speculative point of view, but it could probably be considered not enough to change the standard approach to the patient with moderate to severe cancer pain. Likewise, three trials and one meta-analysis report a significant preference of the patient for transdermal fentanyl, suggesting a more favourable impact on the quality of the life of the patient and introducing a novel factor to influence the risk/benefit ratio in favour of transdermal opioids. Unfortunately, even when we consider the treatment impact on the quality of life, the quality of the data is extremely poor due to the use of not validated and often questionable tools. Moreover, most of the selected trials are based on an extremely modest design, and the statistical power is absolutely inadequate to demonstrate any benefit of the experimental arm when compared with oral morphine.

All these considerations can be well analysed using the GRADE system to formulate the final recommendations for the clinical practice. Although the trial designs could suggest a high level of evidence in the traditional statistical and hierarchical classification criteria, the final result for the single trials becomes low or very low (as detailed in Table 3), and the results of the comprehensive analysis to answer the three questions are low for transdermal opioids (without distinction between transdermal fentanyl or buprenorphine) and transdermal fentanyl, and they are very low for transdermal buprenorphine.

The risk/benefit ratio represents another critical aspect of the problem. As both the analgesic effect and the impact on quality of life have only a minor significance in defining the benefit of transdermal opioids or oral morphine, all our considerations about the risk/benefit ratio need to be based on the safety profile of the two strategies, and what really emerges from our systematic review is a significant difference in the safety profile of the two strategies. On the whole, basing our considerations on the two meta-analyses, transdermal opioids are better than oral morphine for constipation, and a differential safety profile can be identified for transdermal opioids (with lower occurrence of constipation and urinary retention) and oral morphine (with lower occurrence of nausea, sweating and diarrhoea). Although combined with a significant reduction of laxative use or with the preferences of the patient, which favour the use of transdermal opioids, all these data are probably inadequate to influence the risk/benefit ratio in favour of transdermal opioids, and a comprehensive assessment of the risk/benefit ratio remains uncertain between transdermal opioids (fentanyl or buprenorphine) and oral morphine.

All these considerations probably support our work conclusions, which can be summarized as follows according to the three preliminary questions.

1. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids what is the evidence that transdermal opioids are better than oral morphine?
   a. Quality of the evidence: low.
   b. Risk/benefit ratio: uncertain.
   c. Strength of the recommendation: uncertain trade-offs.

2. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, what is the evidence that transdermal fentanyl is better than placebo or other oral/transdermal opioids in the management of pain?
   a. Quality of the evidence: low.
   b. Risk/benefit ratio: uncertain.
   c. Strength of the recommendation: uncertain trade-offs.

3. In adult patients with moderate to severe pain directly due to cancer and never treated with strong opioids, which is the evidence that transdermal buprenorphine
is better than placebo or other oral/transdermal opioids in the management of pain?

a. Quality of the evidence: very low.
b. Risk/benefit ratio: uncertain.
c. Strength of the recommendation: no net benefit.

Consequently, to date no definitive data exist to support an extensive use of transdermal opioids in all strong-opioid naive patients with moderate to severe cancer pain, and no literature data probably justify the extensive use of transdermal formulations reported in clinical practice by several authors.8–11 Oral morphine (and not the oral formulations obtained from different opioids), although supported by as modest evidence as those supporting transdermal opioids, probably remains the treatment of choice for moderate to severe cancer pain in opioid naive cancer patients, and transdermal opioids represent a valid alternative when the oral route or oral morphine are not suitable. Likewise, although the published data comparing transdermal fentanyl with transdermal buprenorphine are limited, the lower level of evidence supporting transdermal buprenorphine can probably differentiate the two molecules in favour of transdermal fentanyl. Further data are surely necessary to modify this kind of approach, which is based on the actual evidence of efficacy and safety of transdermal opioids when compared with slow release oral morphine.

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References